

Endocrine

Introduction

100 trillion cells

- Coordination of body functions by chemical messengers: 7
 - 1 Endocrine hormones are released in BLOOD and affect remote cells (slow mechanism)
 - 2 Paracrine hormones are released in the extracellular fluid and affect nearby cells
 - 3 Neurotransmitters are released at synapses (rapid mech)
 - 4 Neuroendocrine hormones are released by neurons in the blood (intermediate mechanism)
 - 5 Autocrines affect the cells that produce them via ECF
 - 6 Cytokines: Peptides secreted into the extracellular fluid
They function as autocrine, paracrine or endocrine hormones
e.g. interleukins from helper cells & leptin from adipocytes
 - 7 Direct communication through gap junctions in between contiguous cells of the same type.

Endocrine glands

- Pituitary gland is the master gland. Ant. pituitary controls
- 3 endocrinal glands thyroid, adrenal cortex and gonads:
- 3 " " " not controlled by pituitary; parathyroid, adrenal medulla and pancreas.

Organs with endocrine functions in addition to their usual functions

- 1 Heart: Atrial natriuretic peptide ANP.
- 2 Kidney: Erythropoietin, renin & 1,25(OH)₂ cholecalciferol.
- 3 Liver: Somatomedins & 25(OH) cholecalciferol.
- 4 Skin: Calciferol (Vitamin D₃).
- 5 Gastro-intestinal hormones: refer to digestion

Endo
①

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● Inter-relation between endocrine and nervous system

Ⓐ The nervous system can affect the endocrine system :

① Hypothalamo-hypophyseal portal circulation

Exists between the hypothalamus and the anterior pituitary.
Carries releasing & inhibiting hormones from ventromedial, arcuate, preoptic and paraventricular nuclei.

② Hypothalamo-hypophyseal tract :

Exists between the hypothalamus and the posterior pituitary.
Carries ADH & oxytocin to be stored in posterior pituitary.

③ Direct connection between hypothalamus & adrenal medulla

It controls epinephrine & norepinephrine secretion.

Ⓑ The endocrinal system also affects the nervous system

Pathomone & thyroxine affect the excitability of the nervous system.
e.g. ++ $\rightarrow$ ++ serum Ca^{++} $\rightarrow$ -- excitability.

● Characters of endocrinal hormones :

- ① They are secreted directly in blood in small amount (very active).
- ② Some hormones have generalised actions e.g. growth & thyroxine;
others affect specific target organs e.g. sex hormones & ACTH.
- ③ Hormones are removed either by target cell uptake,
metabolic inactivation by liver or excretion by kidney.
- ④ Hormones play a key role in regulating almost all body functions, including metabolism, growth, development, water and electrolyte balance, reproduction and behavior.
e.g. -- growth hormone $\rightarrow$ dwarfism
-- thyroxine $\rightarrow$ -- metabolism
-- insulin $\rightarrow$ -- glucose utilisation
-- sex hormone $\rightarrow$ -- sexual function

Endo
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Chemical Structure & Synthesis of hormones:

Lipid insoluble

① Ptn & polypeptide
Most hormones

Pituitary

Pancreas

Parathyroid

3 ← Peptides (100) → 200 aa
Activation of enzymes

Rapid action (Minutes)

Soluble in lipid

② Steroid

Sex hormones

- Gonads

- Adrenal cortex

Simple diffusion

Synthesis of enzymes

Slow action (Hours or days)

Epinephrine 80% ③ Tyrosine
Norepinephrine 20% one aa
like ptn hormones

T₃ & T₄

like steroid hormones

• Granular ER (ribosomes)
Pre pro hormone (large ptn)
pro hormone inactive

• Golgi apparatus
Packaging as secretory vesicles
cleavage → hormone active

• Release Exocytosis
- Mainly by ++ Ca⁺⁺
- or ++ cAMP
→ activate ptn kinase
→ ++ Hormone secretion

Steroids are formed
from Cholesterol.

very little storage
(not like T₃ & T₄
or ptn & peptides)

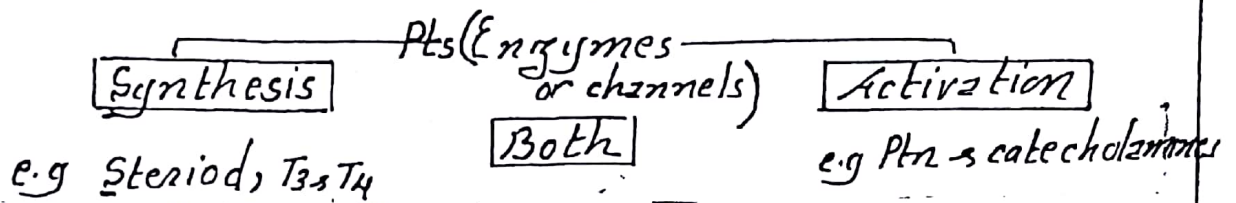
Carried on plasma ptn
mainly globulins
(high affinity)

Free hormone
Active

Lipoptn
Inactive
End

③

Mechanism of action of hormones



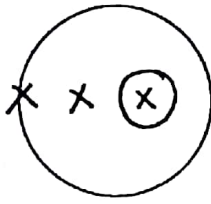
Hormone receptors and their activation :

- 1 1st step of hormone action is union with specific receptors
- 2 Hormone - receptor complex → cascade reactions
- 3 Large protein molecule located at

Membrane (on outer surface) e.g

Cytoplasm e.g

Nucleus (on chromosomes i.e DNA) e.g



ptn H & catecholamines

steroid hormone, T₃ & T₄
- 4 Dynamic structure number is not constant

Down regulation

with ++ Hormone conc.

Causes

- 1 inactivation of receptor
- 2 intracell. Ptn. signaling mol.
- 3 internalisation (temporary sequestration to cell inside)
- 4 Destruction of internalised R.
- 5 -- production of R.

Up regulation

With -- hormone conc.

- 1 ++ receptor expression
- 2 -- internalisation.

End

Hyperfunction

Gigantism (rare)

Acromegaly

Before

← union of epiphysis →

After

Acidophilic

Symmetrical overgrowth

 overgrowth

- | | |
|---|---------------------------------|
| 1 | <u>All</u> bones (proportional) |
| 2 | <u>All</u> soft tissues |

- 2 All soft tissues
- splenomegaly
 - ms early st
 - later weak

- 3 Hyperglycemia
DM in 10%.

4. Hypogonadism.

- 5 Panhypopituitarism



- 1 Terminal portions of skeleton
Hand & foot, skull, vertebrae

2. Skin, Muscle & other soft tissues.
Pit, thyroid, viscera & breast
↳ Bitemporal hemizygia

- 3 Hyperglycemia, glycosuria
secondary DM

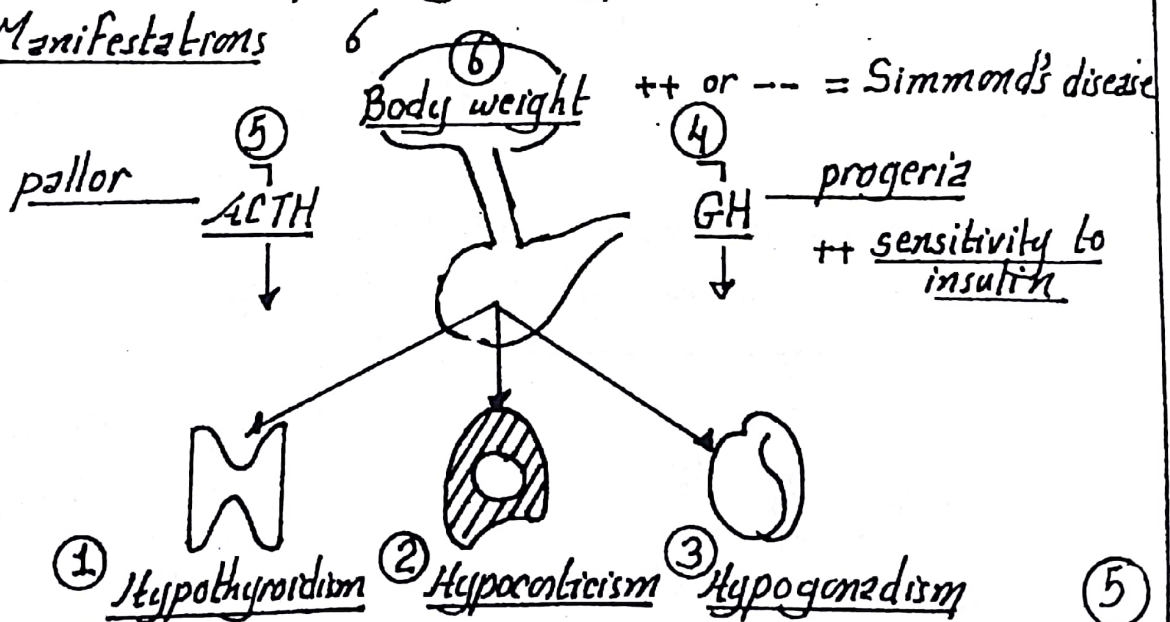
- 4 Meg Acromegalic giant



Panhypopituitarism

Causes 2 ♀ severe postpartum hge i.e. Sheehan's syndrome
♂ pituitary or hypothalamic tumour

Manifestations



● Mechanism of action of hormones

- Hormone receptors Discussed before
- Intracellular signaling Hormone is 1st messenger
 - A hormone (ligand) affects its target tissues by first forming a hormone-receptor complex
 - Activated receptor i.e. $H-R$ complex initiates either

Ptn Synthesis
i.e. Genomic action
Lipid Soluble H.
e.g. Steroids; T_3 & T_4

Ptn activation
i.e. Non-genomic action
Lipid insoluble hormones
Ptn, peptide hormones
Catecholamines
Serotonin & melatonin

Note: Ptns are either enzymes or ion channels

Non genomic action e.g. ptn, peptide H & Catecholamine

Receptors In or on the surface of cell mem. (lipid insoluble)

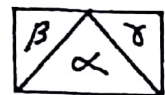
H-R complex regulates activity of target ptns either
a through coupling with G ptn i.e. G ptn coupled receptor
b or directly i.e. Enzyme linked receptor

[1] G ptn linked hormone receptors indirect action

G ptns

- Regulatory ptns. 1000 known G ptns coupled receptors
- Groups of cell membrane ptns called.

Hetero trimeric GTP binding ptns



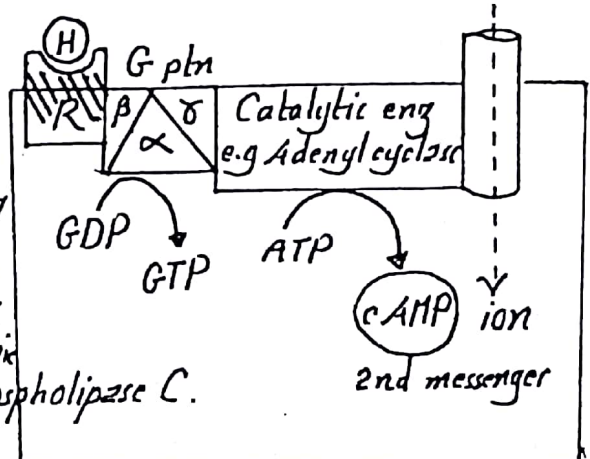
include 3 trimeric parts α , β & γ subunits

- Inactive G ptn binds GDP on α subunit
- Activated G ptn (by H-R complex) exchanges its GDP by GTP

Encl

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- α subunit to which GTP is bound
- dissociates from trimeric complex
- & associates to intracellular signalling proteins which either
 - 1 Open or close cell membrane ion channels
 - 2 or change the activity of cytoplasmic enzymes e.g. adenylyl cyclase or phospholipase C.



Receptors coupled with G ptn have

seven transmembrane segments that loop in & out of the cell membrane.

a the cytoplasmic tail of R. is coupled to G ptn.

b the extracellular part of R. binds to the ligand (hormone).

When the hormone is removed the α subunits

- inactivates itself by converting its bound GTP to GDP
- & combines with the β & δ subunits

Depending on the coupling of hormone receptor to an.

- stimulatory G ptn (G_s ptn) $\rightarrow$ ++ activity of intracellular enzymes
- inhibitory G ptn (G_i ptn) $\rightarrow$ -- " of " enzymes

2 Enzyme linked hormone receptors

Some receptors, when activated, function

- Directly as enzymes.
- or activates closely associated enzymes either directly or through activation of second messenger systems which includes
 - 1 - cAMP
 - 2 - cell membrane phospholipids
 - 3 - Calcium calmodulin system
 - 4 - cGMP

Characters of the receptors linked to enzymes:

- a They pass through the membrane only one time
- b They have their hormone binding site on the outside of the cell membrane
- c They have their enzyme binding (catalytic) site on the inside of the cell membrane

When the hormone binds to this receptor the enzyme inside the cell is immediately activated

Second messenger systems 4

a) Adenyl cyclase - cAMP:

cAMP is related to 3 enzymes

① cAMP is formed by ADENYLYL CYCLASE

1st mechanism When the hormone binds with a special transmembrane receptor; the receptor end that protrudes inside the cell becomes the activated adenylyl cyclase.

Another mechanism When the hormone binds with the receptor, the receptor binds to a G protein.

- Stimulating G pln (Gs pln) stim. adenylyl cyclase.

- Inhibiting G pln (Gi pln) inhibits adenylyl cyclase

Activated adenylyl cyclase converts ATP to cAMP

② cAMP is destroyed by PHOSPHODIESTERASE

Drugs which inhibit phosphodiesterase $\rightarrow$ ++ cAMP

$\rightarrow$ potentiate action of hormones acting via cAMP

③ cAMP activates cAMP dependent Pln kinase A

This enzyme phosphorylates specific cell proteins

$\rightarrow$ biochemical cell reactions i.e. hormone response.

b) Cell membrane phospholipids:

Some hormones activate transmem. receptors that activate the enzyme phospholipase C

$PIP_2 \xrightarrow{\text{Phospholipase C}} IP_3 + DAG$

Phosphatidyl inositol
biphosphate

Inositol triphosphate
Diacylglycerol
second messengers

① IP_3 (C_{45}) mobilises Ca^{++} from mitochondria & E. reticulum.

Calcium ions have their own second messenger effects.

e.g. smooth muscle cont. or change of cell secretion

② DAG (lipid) activates protein kinase C

This enzyme phosphorylates specific cell proteins

Again the lipid portion of DAG is arachidonic acid

$\rightarrow$ prostaglandins & other local hormones

$\rightarrow$ multiple effects

end
⑦

Hormones that use cAMP as second messenger	Hormones that use IP_3 & DAG as second messenger
- Tropic hormones of pit. TSH, ACTH, FSH & LH - Beta receptors of Catecholamines - Vasopressin & receptors of ADH - Angiotensin II & Calcitonin - Parathormone (PTH) - Human chorionic gonadotropin. HCG - Glucagon, Somatostatin & secretin	- Releasing hormones of hypoth. GHRH, GnRH, TRH (not CRH) - Alpha receptors of Catechol. - Vasopressin & receptors (V_1) - Angiotensin II - Oxytocin

[c] Calcium - Calmodulin :

Opening of Ca channels & Calcium entry is initiated by:

- 1 Changes in membrane potential (voltage gated channels).
- 2 Hormone interaction with membrane R (ligand " ")

When normal Ca^{++} ion conc. is increased from 10^{-8} or 10^{-7} mol/L to 10^{-6} or 10^{-5} mol/L, Ca^{++} activates calmodulin system.

Calmodulin is a Ca^{++} binding ptn which has 4 Ca^{++} sites. When " binds to Ca^{++} , calm. changes its shape & initiates multiple effects inside the cell. including activation or inhibition of ptn kinases.

[d] cGMP: cyclic guanosine monophosphate.

Few peptide hormones e.g ANP act via cGMP, which is slightly different from cAMP

Hormones that act mainly on the Genetic machinery of the cells i.e Genomic action.

[1] Steroid hormones ++ Ptn synthesis & activation of Genes e.g Adrenal, gonadal steroids & vitamin D

These hormones are lipid soluble

They enter the cell by simple diffusion.

They interact with cytoplasmic receptors.

End
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The activated H-R complex then binds with a specific regulatory (promoter) sequence of the DNA called HORMONE RESPONSE ELEMENT → activation or repression of transcription of specific gene → formation of mRNA → protein synthesis (enzymes, transport proteins or structural proteins).
 The response is determined by: - the specificity of receptors
 - The specificity of the gene regulated by receptor.

[2] Thyroid hormones ++ gene transcription in the cell nucleus

These hormones bind with NUCLEAR receptor (within the chromosomal complex) to control genetic promoters or operators.
Two important features of thyroid hormones function in the nucleus

- a they activate genetic mechanism for the formation of more than 100 intracellular proteins. Many of these are enzymes that ++ metabolic activity of almost all body cells
- b One bound to the intranuclear receptors, they express their control functions for days or even weeks

Transport of hormones in the blood

- 1 Proteins, peptides & catecholamines (H_2O soluble) are dissolved in plasma
- 2 Steroid & thyroid hormones (lipid soluble)
 - less than 10% exist in the free form (ACTIVE form)
 - Mainly bound to plasma proteins (mostly to globulins).
 - serve as reservoirs for the free hormones.
 - slow their clearance from plasma.
 - ++ their solubility in plasma (H_2O).

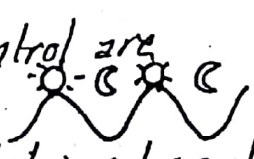
Feedback control of hormone secretion

- [1] -ve feedback prevents overactivity of hormone system
 - The hormone or one of its products has a -ve feedback effect to prevent oversecretion of the hormone & ensures a proper level of hormone at target tissues.
 - -ve feedback occurs at all levels including gene transcription & translation i.e. synthesis or storage.

According to distance between site of hormone secretion & site of feedback effect, there are 3 types of feedback:

Type of Feedback	LONG loop	SHORT loop	Ultrashort loop
Site of hormone	endocrine glands	ant. pit	Hypothalamus
Site of feedback	ant. pit. or hypoth.	Hypothalamus	Hypothalamus

- [2] +ve feedback causes surge of hormone secretion: rare
 e.g. preovulatory LH surge which causes ovulation
 ++ estrogen from ovaries $\rightarrow$ ++ LH from ant. pit
 ++ LH $\rightarrow$ ++ estrogen from ovaries $\rightarrow$ ++ LH
 $\rightarrow$ ovulation then -ve feedback occurs.

- [3] Cyclic variations in hormone release
 Superimposed on -ve & +ve feedback control are
 periodic variation in hormone release. 
Cause seasonal changes, aging, diurnal (daily) cycles & sleep

The pituitary gland (hypophysis cerebri) 1cm 1g

The pituitary gland is composed of:

1- adenohypophysis which originates from the roof of the mouth (Rathke's pouch).

It is composed of:

A) anterior lobe from the anterior part of the pouch

B) intermediate lobe (rudimentary in humans) from the posterior part of the pouch

2- neurohypophysis (posterior pituitary gland) which originates from the floor of the hypoth. i.e. neuronal tissues.

Adenohypophysis Anterior pituitary

Ant pit. secretes Six important polypeptides & glycoprotein hormones

Hormone	Cells	%	Ch. nature
1 Growth H (somatotrophic H).	Somatotropes	30-40	Polypeptide
2 ACTH (corticotrophin)	Corticotropes	20	Polypeptide
3 TSH (thyrotrophin)	Thyrotropes	3-5	glycoprotein
4 Prolactin (PRL)	Lactotropes	3-5	Polypeptide
5 FSH] (gonadotropins)	Gonadotropes	3-5	glycoprotein
6 LH]			

Note 13 lipofropin LPH (less import) is secreted by corticotropes

Control of secretion of anterior pituitary

1 Hypothalamic control

- via releasing and inhibiting hormones :

1 GHRH GROWTH H. RELEASING H. more in children.

2 GHIH GROWTH H. INHIBITING H. = somatostatin more in adult.

3 PIH PROLACTIN Hormone

4 TSH RH = TRH Thyrotropin RH .

5 ACTH RH = CRH Corticotropin RH .

6 FSH RH] GRH Gonadotropin RH .

7 LH RH]

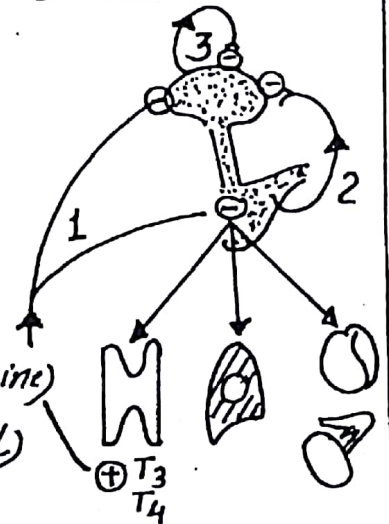
- Characters 1 Small ^{poly} peptide (except PIH is dopamine)

2 Nonspecific (TRH + TSH, GH, PRL)

3 Mode of action via cAMP

- Site of release Neurones of MEDIAN EMINENCE of hypoth.

- Mode of delivery Hypothalamic-Hypophyseal PORTAL CIRCULATION
Between 2 sets of capill. (1st in hypoth, 2nd in ant. pituitary)



2 Feed back control

- 1 Long loop : Target endocrinal g. hormones on [Pituitary or Hypothalamus]
 a Mostly inhibitory i.e. -ve feed back
 b May be +ve FB e.g. estrogen $\rightarrow$ ++ LH & LH $\rightarrow$ ++ estrogen

- 2 Short loop : Pituitary hormones on hypothalamus
Always inhibitory i.e. -ve feed back.

- 3 Ultrashort : (short-short loop) Hypoth. RH & LH on hypoth. end
Always inhibitory i.e. -ve feed back.
Autocrine

Growth hormone GH = Somatotropin = Somatotrophin hormone

• Chemical nature :

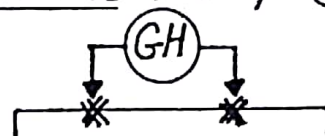
- Ptn hormone 191 aa MW (22 K) hGH.

- May variant hGH (20 K) & desaminoforms. Less active

• Site of release : Somatotropin ACIDOPHILIC cells of ant pit (30-40%)

• Mechanism of action JAK₂ STAT

i.e nongenomic & genomic



ONE GH molecule binds to TWO GH receptors forming HOMODIMER.

H-R complex activates JAK (Janus Family of Tyrosine Kinases)

These tyrosine kinases → autophosphorylation and
phosphorylate other substances resulting in :

- [a] Activation of membrane protein kinase C & phospholipase C.
- [b] Phosphorylation of insulin receptor substrate IRS
(intermediary product of metabolic pathway induced by insulin)
- [c] Phosphorylation of Signal Transducer and Activation of Transcription (STAT) ptns → pbn synthesis (genomic action)

Physiological Functions (Actions) of GH

Exerts its effect on almost all tissues (not target glands)

It has two main actions insulin like & antiinsulin actions

1 Metabolic effects

a Ptn Anabolic

b CHO Diabetogenic

c FAT Lipolytic ketogenic

2 Effects on growth.

Anabolic + Growth

Diabetogenic + Lipolytic ketogenic = Insulin like actions
= Antiinsulin actions

1 Metabolic effect

(a) Ptn

Anabolic

GH ++ number & size of cells

1 ++ aa uptake and transport through cell membrane.

2 ++ RNA translation & ++ mRNA & ++ transcription of DNA.

3 Ptn sparing effect ++ FFA production of energy

(b) CHO

Diabetogenic

GH ++ bl. glucose via 1, 2, 3

1 -- glucose uptake in sk ms & fat cells by -- hexokinase.

2 -- glucose utilization by -- glycolysis & oxidation of glucose.

3 ++ glucose production by liver.

4 ++ glycogenesis

5 ++ insulin secretion due to GH induced insulin resistance caused by ++ fatty acids in blood which -- insulin action.

N.B. If GH secretion ++ more than 100% → Diabetes Mellitus.

In absence of insulin, GH fails to cause growth.

explanation Insulin ++ transport of some aa into cells

(c) FAT

Lipolytic ketogenic

1 ++ Lipolysis in adipose tissues → Hyperlipidemia

2 ++ Fatty acid uptake & ketone body formation by liver

N.B. excess GH → Ketosis (++ acetoacetic acid formation)

2 Effect on Growth

GH ++ ptn synthesis, cell division & proliferation of many tissues
On soft tissues GH stim. growth of all soft tissues

stimulates erythropoiesis and produce +ve nitrogen balance.

On bone and cartilage GH stim. growth of skeletal frame.

• ++ ptn deposition by chondrocytic & osteogenic cells.

• ++ reproduction of chondrocytic & osteogenic cells

• ++ conversion of chondrocytes into osteogenic cells.

Two principal mechanisms of bone growth:

- ① Before bone fusion (adolescence), GH ++ length of long bones by stimulating deposition of new cartilage & bone at epiphyseal cartilage.
- ② Throughout life, GH ++ thickness of all bones especially membranous bones by stimulating osteoblasts in bone periosteum.

GH stimulates cartilaginous growth at the epiphysis indirectly viz somatomedins (insulin like growth factors) Pbn with MW 4500-7500.

Proof GH doesn't stimulate chondrocytes outside the body.

At least 4 somatomedins, the most important is somatomedin C (IGF₁) GH can ++ formation of IGF₁ in local chondrocytes to cause local growth. Chondrocytes ++ collagen & chondroitin sulphate (matrix of cartilage). Somatomedins was called sulfation factor.

SOMATOMEDINS : = Insulin like growth factor IGF

- GH ++ „ production by the LIVER & other tissues
Glucocorticoids & pbn deficiency -- somatomedins
- Ch. nature polypeptides resemble proinsulin
- Receptors closely resemble insulin receptors
- Action on CHO & fat = insulin.

	GH	IGF ₁
<u>Duration of action</u>	Short	Long
<u>Plasma pbn binding</u>	Weak	Strong
<u>Half-life</u>	Less than 20 min	about 20 hours

Regulation (control) of GH secretion :

Normal level : Adult 2-4 ng/ml bl. Child 5-8 ng/ml

GH is secreted in : Pulsatile pattern.

GH secretion is under 2 main controlling systems:

[1] Hypothalamic control : The ventromedial nuclei of median eminence secrete GHRH & GHIH (less important)

[2] Feedback control

a Long loop feedback IGF₁ from the LIVER acts on

- Hypothalamus ++ somatostatin → -- GH secretion

- Anterior pituitary -- GH secretion (direct action)

b Short loop feedback GH inhibits both GHRH & GHIH

c Ultrasort loop feedback GHRH inhibits itself

GH secretion is stimulated (increased) by :

1 Starvation especially with severe ptn deficiency

2 Fasting Hypoglycemia or -- fatty acids in blood

3 Sleep GH ++ during 1st 2 hours of deep sleep stages II & IV

4 Stress & excitement

→ 5 exercise

→ 6 trauma

7 GHRH

8 Sex hormones : estrogen & testosterone

GH secretion is decreased by :

1 ++ blood glucose.

2 ++ blood FFA.

3 Obesity

GHIH (somatostatin).

5 exogenous GH.

6 cortisol (catabolic hormone) i.e antagonist

7 aging

Disturbance of GH Function

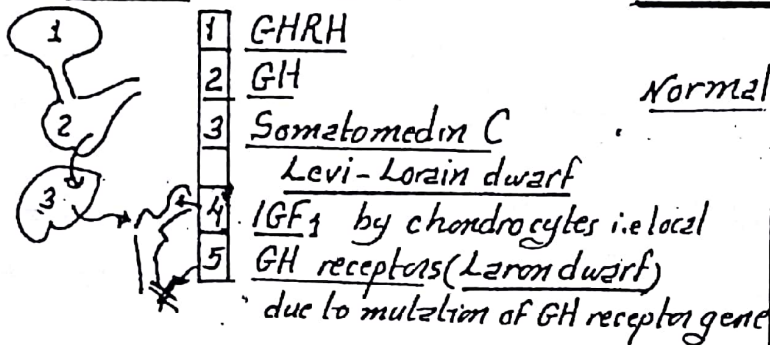
Primary: Pituitary in origin

Hypo or Hyperfunction
Secondary: Hypoth. in origin

• Hypo function:

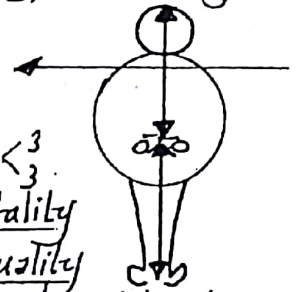
A Pituitary dwarfism

Causes: Decreased



Characters: $6 < \frac{3}{3}$

Normal $\left\{ \begin{array}{l} \text{Mentality} \\ \text{Sexuality} \\ \text{Physical} \end{array} \right.$ until 4th year
100-120 cm.
Short stature trunk & limb
but well proportioned
i.e. span = height
vertex to symphysis
" " to heel
Psychological unstable
May Delayed puberty



B Pituitary infantilism

= Pituitary dwarfism (-- GH)
+ Hypogonadism (-- Gonadotropins)

Differential diagnosis:

① Achondroplastic Dwarfism Most common form of dwarfism.

Cause autosomal dominant mutation of the gene for
Fibroblast growth factor receptor-3 $FGFR_3$

Characters Trunk (head, neck & chest) normal.
Limbs short i.e. disproportion.

② Thyroid dwarf (cretin)

Cause -- thyroid hormones during infancy

Characters Physically dwarf disproportion (Bones) soft t.
Mentally idiot.
Sexually sterile & impotent.

Ht: Human GH synthesised by *Escherichia coli* bacteria
by recombinant DNA technology

• Hyperfunction:

A Gigantism (Giantism)

rare

Cause ++ GH before union of epiphysis (adolescence)
due to acidophilic adenoma.

Characters
① Symmetrical overgrowth of all bones (normal proportions) 16

- ② Symmetrical overgrowth of All soft t. (^{indicated by} ++ 4OH proline in urine).
- Splanchnomegaly.
 - Muscles: 1st strong later on very weak (due to overstretch.)
- [3 Hyperglycemia & glycosuria & DM develops in 10% of cases
- [4 Hypo gonadism due to p. on. basophils secreting gonadotropins
- 5 Ends in panhypopituitarism & death (due to destruction of all pit. cells)
- ltt Microsurgical removal of the tumour or irradiation of pit.

13] Acromegaly Acro = extremities Megaly = large

Cause ++ GH after union of epiphysis (after puberty).

Characters:

- 1] Overgrowth of terminal portions of the skeleton:
- Hands & feet: Large & thick (Pt needs larger shoes)
 - Skull: Flat bones produces acromegalic facies
Box shaped skull
Prominent: ciliary ridges, nasal bones & cheeks
Mandible: prognathism (protruded) & teeth separation
 - Vertebral column: Kyphosis → Ape like posture
- 2] Skin, muscle and other soft tissues:
- Face overgrowth of nose & lips
 wrinkling of scalp & forehead skin → bulldog facies.
 - Pituitary enlargement may press on optic chiasma
 → bitemporal hemianopia (tubular field).
 - Thyroid enlargement → goitre &
 increased production of T₃ more than T₄.
 - Overgrowth of viscera.
 - Muscles 1st strong later weak due to overdeveloped bones & viscera
 - Gynecomastia & Milk production in ♂ (GH = Prolactin)
 - Hyperglycemia & glycosuria &
Secondary DM due to exhaustion of beta cells of pancreas
- 3] Acromegaly may occur on top of gigantism if the later is not treated
- 4] Acromegalic giant.

Prolactin = Mammotropine = Lactotropine PRL

- Ch. nature: Polypeptide 199 AA similar in structure & function to GH
- Site of release: Ant. pit (lactotropes) + endometrium & placenta (pregnancy)
- Plasma level: ♂ 5 ng/ml ♀ 8 ng/ml.

PRL ++ by Sleep at its onset & persists at a plateau.
Pregnancy it ++ gradually & peaks at parturition.
Suckling produces a surge which -- after 3 months of nursing. In non pregnant ♀, nipple massage causes mild ++ in PRL.

- Mechanism of action: similar to GH discuss JAK STAT
PRL receptors resemble GH receptors.

Actions of prolactin:

- ♀ 1 Breast priming breasts with estrogen & progesterone.
++ milk production of casein & lactalbumin.
- 2 Ovaries -- effect of gonadotropins → prevents ovulation.
so amenorrhoea & infertility during lactation.
- ♂ unknown physiologic effect.

Regulation (control) of PRL: + Factors ++ PRL

- 1 Hypothalamus controls PRL secretion mainly by
 - Prolactin inhibiting hormone PIH (dopamine in nature)
→ tonic inhibition of PRL during non lactation periods
 - Prolactin stimulating hormone not definitely present.
- 2 Indirect -ve feed back ++ PRL → ++ PIH → -- PRL.

Disturbance of PRL secretion:

- hypoprolactinemia rare. It occurs in ♀ due to pit. damage.
Ht Dopamine receptor blocker e.g chlorpromazine.
- Hyperprolactinemia Mostly caused by pit. tumour.
Effect ♀ breast: galactorrhoea in a nonlactating period.
 ♀ Ovaries: infertility & amenorrhoea.
 ♂ breast: gynecomastia (enlargement of breasts)
 ♂ Testes: infertility (due to -- action of gonadotropin)
 ♀ -- Libido.
Ht Dopamine agonists e.g bromocriptine → -- PRL

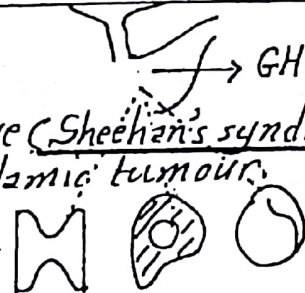
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- Ch. nature: Polypeptide 199 AA similar in structure & function to GH
- Site of release: Ant. pit (lactotropes) + endometrium & placenta (pregnancy)
- Plasma level: ♂ 5 ng/ml ♀ 8 ng/ml.
 - PRL ++ by Sleep at its onset & persists at a plateau.
 - Pregnancy it ++ gradually & peaks at parturition
 - Suckling produces a surge which -- after 3 months of nursing. In non pregnant ♀, nipple massage causes mild ++ in PRL.
- Mechanism of action: similar to GH. discuss JAK STAT
PRL receptors resemble GH receptors.
- Actions of prolactin:
 - ♀ 1 Breast priming breasts with estrogen & progesterone.
++ milk production of casein & lactalbumin.
 - 2 Ovaries -- effect of gonadotropins → prevents ovulation.
so amenorrhoea & infertility during lactation.
 - ♂ unknown physiologic effect.
- Regulation (control) of PRL: + Factors ++ PRL
 - 1 Hypothalamus controls PRL secretion mainly by
 - Prolactin inhibiting hormone PIH (dopamine in nature)
→ Tonic inhibition of PRL during non lactation periods
 - Prolactin stimulating hormone. - not definitely present.
 - 2 Indirect -ve feed back ++ PRL → ++ PIH → -- PRL.
- Disturbance of PRL secretion:
 - Hypoprolactinemia rare. It occurs in ♀ due to pit. damage.
Ht Dopamine receptor blocker e.g chlorpromazine.
 - Hyperprolactinemia Mostly caused by pit. tumour.
Effect ♀ breast: galactorrhoea in a nonlactating period.
 Ovaries: infertility & amenorrhoea.
 ♂ breast: gynecomastia (enlargement of breasts)
 Testes: infertility (due to -- action of gonadotropins)
 ♀ -- Libido.
 - Ht Dopamine agonists e.g bromocriptine → -- PRL

Panhypopituitarism =

- Causes: ♀ severe postpartum hemorrhage (Sheehan's syndrome)
 ♂ Pituitary tumour or hypothalamic tumour.
 - Manifestations: $6 < 3$
- 1 Hypothyroidism: -- BEE & anemia.
 - 2 Hypocorticism: Hypoglycemia, Hypotension & generalised weakness.
 - 3 Hypogonadism: ♀ Amenorrhea ♂ impotence & sterility.
 - 4 -- GH ++ sensitivity to insulin
 Generalised premature rapidly progressing senility (progeria)
 - Premature graying of hair - loss of teeth
 - Dry wrinkled skin - Shrunken hands feet.
 - 5 -- ACTH marked pallor (also caused by anemia)
 - 6 Body weight a may ++ (due to -- lipolysis of GH, Cortisol, T_3).
 b or -- (due to damage of feeding centre in hypoth (Simmonds' dis))



Post. pituitary = Neurohypophysis

brain 3rd vent

- Post. pituitary stores & releases 2 hormones:
 - 1 ADH = Vasopressin = pressophysin = arginine-vasopressin
 - 2 Oxytocin = Pitocin = oxyphysin
- Chemistry: Nonpeptide (9 AA)
- Formed: In hypoth: by megacellular neurones (supraoptic & paravent. nuclei as prepro-pressophysins prepro-oxyphysin.
- Migration & storage: Packaged in secretory granules as propressophysin & prooxyphysin. Then migrate in neuronal axis of hypoth. hypoph. tr. & undergo cleavage & transformation into.
 - pressophysin and neurophysin II
 - oxyphysin and neurophysin I
- Release by action potential by Ca^{++} dependent exocytosis



ADH (Antidiuretic hormone) = [Vasopressin]

Formed: mainly by Supraoptic nuclei in hypoth.

Released into brain 3rd ventricle (function is unknown)

Median eminence cosecreted with CRH → hypoth. hypoph.
portal circ. to corticotropes of ant. pit

endo
18

ADH i.e. Vasopressin (V) receptors: G protein couples

- V_1 : VIA to inositol pathway $\rightarrow$ ++ intracell. Ca^{++}
- V_3 : VIB to phospholipase $\rightarrow$ ++ prostaglandins
- V_2 to adenylyl cyclase $\rightarrow$ ++ cAMP

Functions (actions) of ADH (Vasopressin) 2 x 2

I Renal effects:

- ① Tubular system via $(V_2) \rightarrow$ ++ cAMP (2nd messenger)
 - a Facultative H_2O reab: from late distal tubule (principal cells) & cortical collecting & medullary tubules
Mechanism translocation of H_2O channels (Aquaporin 2)
 - b ++ Urea reabsorption from medullary collecting tubules
Mechanism insertion of urea transporters (UT1)
Effect ++ urea flow to medullary interstitium $\rightarrow$ ++ H_2O reab.
 - c ++ K^+ secretion from cortical collecting tubules to compensate for -- K secretion caused by -- urinary flow.
- ② Renal vascular system via (V_3) in glomerular mesangium
++ local $PG E_2$ (vasodilator) which antagonises the ADH renal VC effect & maintains renal perfusion (local -ve feedback)

II Extrarenal effects:

- ① Vascular system via $(V_1) \rightarrow$ ++ intracell. $Ca^{++} \rightarrow$ intense VC that ++ & maintain ABP in cases of hge.
Note renin-angiotensin-sympathetic n.s are the primary regulator of ABP
- ② In stresses e.g. pain & trauma
ADH & CRH are cosecreted from the paraventricular nuclei
 $\rightarrow$ ++ ACTH secretion via V_3 receptors
 $\rightarrow$ ++ Cortisol secretion (cortisol is antistress hormone)

Control of ADH secretion

I Stimuli that ++ ADH secretion:

- ① ++ plasma osmolality by 1%
Mechanism ++ OP causes outflow of H_2O from cells of End

osmoreceptors. The shrunken cells activate the stretch inactivated cation channels $\rightarrow$ Depol. $\rightarrow$ $+++$ ADH secretion

- (2) -- bl. volume by 10% e.g. hge
Mechanism -- ABP $\rightarrow$ -- inhibitory impulses from:
- the carotid sinus baroreceptors $\rightarrow$ $++$ ADH $\rightarrow$ $++$ ABP
- the low pressure receptors in the atria & big veins via vagi $\rightarrow$ $++$ ADH (this response is weak in humans)
- 3 Beta adrenergic agonists
4 Drugs Morphine, nicotine, some tranquilizers & anesthetics
5 Stress e.g. surgery $++$ ADH via CRH-ADH system for dogs
note Nausea $++$ ADH 500 folds

II Stimuli that -- ADH secretion:

- 1 -- plasma osmolarity.
- 2 $++$ blood volume.
- 3 Alpha adrenergic agonists.
- 4 Drugs: Ethyl alcohol e.g. beer.

Disturbance of ADH secretion:

Diabetes insipidus: Diabetes = large urine vol. Insipidus = tasteless

• Causes:

- 1 Central DI lesion in supraoptic nucleus
Note lesion in hypoth. hypoph. tr or post pit. doesn't produce DI
; because ADH is secreted directly in systemic circulation

2 Nephrogenic DI

- a Congenital defect of renal V_2 receptor (x linked mutation)
- b Non functioning aquaporin 2 (autosomal mutation)

• Manifestations:

- 1 Polyuria $++$ urine vol. up to 10 L/day with low sp. gravity
- 2 Polydipsia However, if thirst sensation is lost $\rightarrow$ Dehydration & death

X Increased ADH secretion Water intoxication

- #### • Causes:
- 1 CNS diseases
 - 2 Ectopic formation of ADH by lung or pancreatic tumour.

- #### • Effects
- 1 -- OP of plasma & ECF
 - 2 Swelling of brain cells $\rightarrow$ headache, nausea, convulsion & death

End
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OXYTOCIN

- Formed : Hypoth. nuclei ; mainly by paraventricular n.

- Functions = Actions

- 1 During suckling Contraction of myoepith. cells around breast alveoli $\rightarrow$ squeezing of milk from breast alveoli into large ducts & nipple.
- 2 During labour Contraction of uterus $\rightarrow$ expel the baby and the placenta
- 3 During sexual intercourse
 - a σ contraction of vas deferens to ejaculate semen
 - b f contraction & relaxation of uterus $\rightarrow$ -- intrauterine p. to help semen transport into the uterus



- Mechanism of action via G ptn $\rightarrow$ ++ IP_3 $\rightarrow$ ++ Ca^{++}

- Mechanism (control) of secretion :

NEUROHORMONAL REFLEX

A Stimulus

- 1 Massage of nipple receptors by suckling or sexual playing i.e. Milk letting or Milk ejection reflex which may be
 - Unconditioned : by receptor stimulation of nipple.
 - Conditioned : i.e. no receptor stim. of nipple. Seeing, hearing or smelling the baby or even thinking about the baby $\rightarrow$ spurting of milk.
- 2 Dilatation of cervix of uterus during labour
- 3 Genital stimulation of σ or f

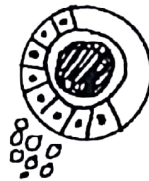
B Afferent Impulses pass through the spinal cord.

C Centre Hypothalamic nuclei

E Efferent Hormone (oxytocin) release from post. pituitary

Thyroid gland

- Highly vascular 5 ml/gm/min.
- Follicles full of colloid (thyroglobulin).



● Hormones:

1) Follicular cells secrete T_4 tetraiodothyronine (thyroxine).
 T_3 triiodothyronine.

2) Parafollicular cells (C cells) TCT thyrocalcitonin

Iodine 500 μ g ingested/day & circulates as iodide I^- .

- 4/5 are rapidly excreted in urine.
- 1/5 is trapped by thyroid for T_3 & T_4 synthesis.

After metabolism of T_3 & T_4 , iodine passes in urine & stool.

Thyrocytes have small reserve of T_3 & T_4 sufficient for min or hours

Follicular cavity has large reserve of T_3 & T_4 for weeks or months

● Functions of Follicular cells:

1) Thyroglobulin synthesis Glycoprotein (670,000 MW)
It is very rich in tyrosine 123 tyrosine/molecule.

2) Formation of T_3 & T_4

① Iodide trapping (pump)

Thyroid cells are -ve relative to interstitium & colloid.

Cotransporter (second active transport) carries Na^+ & I^-

Iodide I^- is carried against conc. & electrical gradient to thyrocyte

N.B iodide trapping occurs in mammary, salivary glands, gastric mucosa & placenta. But unlike thyroid not stim. by TSH

② Oxidation & iodination Peroxidase in thyrocytes:

a oxidises iodide (I^-) with hydrogen peroxide to iodine I_2

b binds iodine to tyrosine of thyroglobulin in 3 & 5 position to form Mono iodo tyrosine MIT.

Di iodo tyrosine DIT.

③ Coupling i.e. binding of tyrosine molecules

- $DIT + DIT \longrightarrow T_4$

- $DIT + MIT \longrightarrow T_3$ & reversed $T_3 \rightleftharpoons T_3 rT$ (inactive)

(22)

Ratio of T_4 , T_3 : rT₃ 40 : 2 : 1.

Release of T_3 & T_4 Apex of thyrocytes ingests thyroglobulin by pinocytosis into vesicles, which traverse cells towards base & merge with lysosomes where:

- Proteinase liberates T_3 , T_4 , DIT & MIT from thyroglobulin.
 T_3 & T_4 diffuse into capillaries.
- Iodotyrosine deiodinase removes iodine from DIT & MIT
iodine is recycled to form T_3 & T_4 .

Storage of thyroid hormones Extra T_3 & T_4 are stored in follicles bound to thyroglobulin (equivalent to body needs for 2-3 months)

● <u>Rate of secretion</u>	70 $\mu\text{g}/\text{day}$	T_4 93%	T_3 7%
<u>Blood level</u>	<u>Total</u>	8-12 $\mu\text{g}/\text{dl}$	0.15 $\mu\text{g}/\text{dl}$
	<u>Bound</u>	99.98 %	99.80 %
	<u>Free</u>	2 ng/dl	0.3 ng/dl

T_3 is more active than T_4 : More free in plasma.
More affinity to receptors 10-15 times

Plasma pln binding. More than 99% is bound
Affinity to globulins (thyroxine binding globulin α_1 & α_2)
is higher than albumin or prealbumin.
Globulins carry $(\frac{2}{3})$ of T_4 and $(\frac{1}{2})$ of T_3 .

● Thyroid receptors 4 types α_1 , α_2 , β_1 & β_2

T_4 binds to 4 types T_3 binds to 3 types (except α_2).

Nuclear receptors close to DNA $\rightarrow$ genomic action

Extranuclear receptors plasma mem, cytoplasm, mitochondria & cytoskeleton $\rightarrow$ nongenomic action e.g. adenylyl cyclase, sugar transport, pyruvate kinase, type II deiodinase & actin polymerization

● Cellular mechanism Regulation of gene expression

- 1 T_3 > T_4 bind to ligand binding domain in TR (thyroid receptor)
- 2 DNA binding domain (helped by nuclear localization signals) binds to DNA $\rightarrow$ transcription $\rightarrow$ ++ mRNA in few min.
 $\rightarrow$ cytoplasmic ribosomes in minutes $\rightarrow$ hundreds of new plns

(23)

These ptns act either directly or indirectly via binding to a new target genes $\rightarrow$ formation of new ptns within hours

Functions (effects) of T_3 & T_4

A Effect on metabolism

① Cell metabolism

- a Mitochondria $\xrightarrow{++}$ size & number $\rightarrow$ $\xrightarrow{++}$ ATP
Uncoupling of oxidative phosphorylation $\rightarrow$ more heat
- b Cell membrane $\xrightarrow{++}$ activity of Na^+-K^+ ATPase $\rightarrow$ more heat

② CHO metabolism $\xrightarrow{++}$ glucose absorption by GIT, glucose uptake, glycolysis, gluconeogenesis & $\xrightarrow{++}$ insulin secretion.

③ Fat metabolism

- a All aspects, lipolysis & FFA oxidation
- b Plasma lipids $\rightarrow$ $\downarrow$ cholesterol due to
- $\cdot \xrightarrow{++}$ secretion of cholesterol in bile & stools
 - $\cdot \xrightarrow{++}$ LDLP receptors in liver $\rightarrow$ $\downarrow$ LDLP in plasma
 - $\cdot \xrightarrow{++}$ secretion of lipoprotein cholesterol by liver cells

④ Ptn metabolism Anabolic However, $\xrightarrow{++}$ T_3 & $T_4 \rightarrow$ catabolism

⑤ Vitamin metabolism $\xrightarrow{++}$ body need for vitamins (coenzymes)

⑥ Basal metabolic rate (basal energy expenditure)

Normal level normal BMR, normal appetite & normal body weight

B Effect on growth Physical, mental & sexual.

a brain development during fetal & first few years

T_3 & T_4 induces neuronal, axonal & nerve ending formation

b Bone & epiphysis normal growth & fusion. (Bones) Soft tissue

c Sexual development normal.

C Body systems

a Primary effect Direct stim. of most body systems

b Secondary effect Calorigenic action T_3 & $T_4 \xrightarrow{++}$ O_2 consumption of almost all tissues except adult-brain, lymph node, spleen, testes & uterus.

Ant. pituitary: O_2 consumption $\downarrow$ due to $\downarrow$ TSH (24)

Regulation of Thyroid gland function

- ① Hypothalamus **TRH** stimulates thyrotropes $\rightarrow$ $+++$ TSH
Mechanism: stimulates phospholipase via G ptn
 $\rightarrow$ $++$ IP_3 & DAG $\rightarrow$ $++$ Ca^{++} $\rightarrow$ release of TSH by exocytosis
- ② Ant. pituitary **TSH** stimulates thyroid cells
Mechanism: stimulates adenyl cyclase via G ptn
 $\rightarrow$ $++$ cAMP $\rightarrow$ activates ptn kinase $\rightarrow$ phosphorylation of ptn
 - a Within 30 min: $++$ proteolysis of thyroglobulin $\rightarrow$ $++$ T_3 & T_4 secretion
 - b Within hours, days & weeks:
 - $++$ formation of T_3 & T_4 $++$ all steps
e.g. $++$ iodide pump i.e. intracell. & extracell. $8:1$
 - $++$ size, number & vascularity of thyroid cells
- ③ Thyroid feed back mechanism: $++$ T_3 & T_4 produces:
 - Direct strong effect on ant. pituitary $\rightarrow$ $--$ TSH
 T_4 is converted to T_3 at ant. $\rightarrow$ to exert its effect
 - Secondary weak effect on hypothalamus $\rightarrow$ $--$ TRH

Disturbance of thyroid function

- hypothyroidism or hyperthyroidism
- Prim. (thyroid), Secondary (pituitary) or Tertiary (hypoth.)

Hypothyroidism:

Causes: Thyroidal or Suprathyroidal

① Thyroidal

- a Congenital absence of thyroid or defect in hormone synthesis
- b Maternally transmitted mother taking antithyroid drugs or excess iodine which $--$ fetal thyroid.
- c Chronic iodine deficiency rare (table salt contains NaI)
- d Chronic thyroiditis due to viruses or antibodies (autoimmu)
- e Iatrogenic overtreatment of hyperthyroidism

② Suprathyroidal Pit causes (second) or hypoth causes (tertiary)

Effects:

I General effects:

- 1 -- Calorigenesis, BEE, body temp which leads to:
 - a ++ susceptibility to cold i.e. Pt can't tolerate cold.
 - b ++ body weight, due to accumulation of myxedematous tissue under the skin (mucopolysaccharides + edema) non pitting
 - c -- activity of all body systems:
 - CVS: bradycardia & -- Cardiac output.
 - Resp: bradypnea.
 - GIT: -- motility & constipation.

2 Skin is coarse, dry & yellow (due to carotinemia).

3 Laboratory findings:

- a INCREASED level of cholesterol in blood.
- b Low T_3 & T_4 with high TSH in blood (thyroid origin).
- c Low T_3 & T_4 with low TSH in bl. (pit or hypoth. origin).

II Specific age dependent effects

- 1 Cretinism Hypothyroidism in infant or early childhood.
 - a Delayed mentally: Idiot (Defective speech incontinence)
 - b Delayed sexually: Impotence and sterile.
 - c Delayed physically: Delay in all milestones of normal growth. Dwarf, Delayed eruption of teeth, delayed closure of fontanelles.
 - d Special facial & body characters
 - Eyes: swollen eye lid with narrow palpebral fissure.
 - Nose: wide nasal bridges.
 - Mouth: enlarged lips & enlarged protruded tongue.
 - Supraclavicular: pad of fat. (triangular with apex upward)
 - Abdomen: pot belly abdomen with umbilical hernia.

2 Myxedema Hypothyroidism in adult

- a -- Mental function: Apathy, drowsiness & ++ reaction time.
 - b -- Sexual function: due to atrophy of gonads
 - c special husky voice & absent outer $\frac{1}{3}$ of eye brows.
- N.B Hypochromic microcytic anemia

Hyperthyroidism 2nd endocrinal disorder after DM.

Causes: thyroidal, extrathyroidal or supratheroid.

① Thyroidal

- a Grave's disease Autoimmune disease. i.e. antibodies against TSH receptors (TSH-R [stim]) Ab. These antibodies which stim. the thyroid are not controlled by TR
- b Acute thyroiditis:
- c Tumour or nodules in thyroid gland.

② Extrathyroidal

- a Ectopic thyroid tissues
- b Excessive intake of thyroid hormones

③ Supratheroid

- a Pituitary tumour of thyrotropes
- b Resistance of pit receptors to T_3 & T_4
i.e. no -ve feedback mech.



Effects:

① ++ BEE +60% to +100% which leads to:

- a Pt does not tolerate hot weather.
- b -- body weight despite ++ appetite (hyperphagia).
- c Skin warm, flushed & sweaty

② Body systems: due to ++ BEE & ++ sensitivity to catecholamine

- a Nervous system stim of RAS → fine tremors in the extended & abducted fingers & Hyperreflexia
- b CVS

++ HR, ++ CO & ++ VR

++ systolic P (due to ++ SV) -- diastolic P (due to VD)
→ ++ pulse pressure.

③ Exophthalmos protrusion of the eyeballs in 50% of Pts

Cause: Cytotoxic autoantibodies against extraocular muscles
→ hypertrophy of extraocular ms & retro orbital connective

Effects: Dryness of eye & rarely optic n atrophy & blindness

④ Goitre: enlargement of thyroid gland

⑤ Laboratory findings

a -- Level of cholesterol in blood.

b High T_3 & T_4 with low TSH in thyroidal & extrathyroidal.

c High T_3 & T_4 with high TSH in supratheroid. (27)

● Antithyroid drugs Goitrogenic drugs

Drugs used in ttt of hyperthyroidism may:

- 1 Interfere with iodide trapping: Monovalent anions which cause competitive inhibition of I (monovalent) pump.
 a Bi-iodate, per-iodate, chlorate, nitrate.
 b Thiocyanates Unlike the above drugs are not taken by follicles.
- 2 Block organic binding of iodide: Thiocarbamides
 Compete with tyrosine & block coupling.
 Drugs 1 & 2 $\rightarrow$ -- T_3 & T_4 $\xrightarrow[\text{back}]{\text{-ve feed}}$ ++ TSH $\rightarrow$ Goitre.
- 3 Medical thyroidectomy radioactive iodine
 It destroys thyroid follicles.

● Goitre

Definition enlargement of thyroid gland.

It is associated with ++, + or normal thyroid activity.



Types:

- Physiological: normal thyroid activity i.e. normal T_3 & T_4
 It occurs in ♀ during puberty, pregnancy or lactation.
- Hypothyroidism: Follicles are full of TG It occurs in
 a severe iodine deficiency
 b inability to secrete or store the formed T_3 & T_4 due to
antibodies TSH-R [block] Ab, T₃ Ab, TRO Ab.
- Hyperthyroidism:
 a Thyroid tumour (adenoma)
 b Grave's disease caused by (TSH-R [stim] Ab)
 c Pituitary tumour of thyrotropes $\rightarrow$ ++ TSH
- Nodular goitre: multiple enlarged nodules which may be
Hot (active) or cold (inactive).

Disorder	Hypothyroidism		Hyperthyroidism	
Lab. finding	thyroidal	suprathyroid	extrathyroidal	suprathyroidal
Cholesterol	++	++	--	--
T_3 & T_4	--	--	++	++
TSH	++	--	--	++
T_3 , T_4 & TSH are measured by radio immuno assay				Endo (28)

★

Calcium

Functions of calcium:

- A ionised calcium : $< 1\%$ non bony calcium.
- 1 Blood clotting
 - 2 Nerve & muscle excitability $\propto \frac{1}{Ca^{++}}$
 - 3 Muscle contractility.
 - 4 Cardiac muscle rhythmicity.
 - 5 Second messenger of some hormones.
 - 6 Secretion of hormones & neurotransmitters by exocytosis
- 
- B Calcium salts : $> 99\%$
- 1 Hard tissues : Bone & teeth.
 - 2 Soft tissues : Milk
 - 3 Storage function.

Distribution of calcium

- A Plasma 9-11 mg/dl $< \frac{1}{2} g$ 3 forms:
- | | | | |
|---|-------|----------------|----------|
| 1 <u>ionised</u> : Ca_2HPO_4, CaH_2PO_4 4:1 | 47.2% | Diffusible | Active |
| 2 <u>complexes</u> : PO_4, HCO_3 & citrate | 6.4% | Diffusible | Inactive |
| 3 <u>bound</u> : mainly to albumin | 46.4% | Non diffusible | Inactive |
- B Bones $> 99\%$ 1100g 2 forms

LABILE calcium	STABLE calcium
Less than 1%	More than 99%
Form: Ca phosphate (amorphous)	Ca hydroxyapatite crystals
Readily exchangeable with plasma	Not readily exchangeable.

NB The liver & intestine can exchange Ca^{++} with plasma (labile)

Absorption of Ca^{++} From GIT

- 30 - 80 % of the ingested Ca is absorbed by upper small intestine by diffusion (passive) or active transport.
- ++ solubility $\rightarrow$ ++ Absorption 4 A
- 1 Acidity HCl.
 - 2 Amino acids i.e. Ptn meal
 - 3 Acidic food product e.g. yogurt
 - 4 Active Vitamin D3 i.e. 1,25(OH)₂ cholecalciferol.
- Endo (29)

NB Citrate forms soluble Ca salts.

Oxalate & phosphorus form insoluble Ca salts.

Minor changes in bl. calcium $\rightarrow$ Dramatic body effects.

Major " in bl. phosphorus $\rightarrow$ little effects.

Phosphorous

500 - 800g

- Bone & teeth 85 - 90%.

- Plasma level 12 mg/dl.

- ATP, cAMP, 2,3DPG & many Ptx are import. for cell reaction.

In ECF, $Ca^{++} \times PO_4^{--} = \text{constant}$ above solubility products
i.e. ECF is supersaturated. Pyrophosphate compound inhibits
the precipitation of Ca^{++} & phosphate. which occurs:

- 1 Physiologically if osteoblasts secrete pyrophosphate inhibitor
- 2 Pathologically in atherosclerosis & degenerated cells

Bone physiology

Bone tissue (special type of connective t.) is formed of:

- 1 Matrix Type 1 collagen ptn responsible for Tensile strength.
- 2 Crystals Hydroxyapatite " " Compression force.
- 3 Cells 3 types osteoBLASTS, osteoCLASTS & osteoCYTES.

1 Osteo blasts

Bone building cells

1 Collagen & other ptns

2 Alkaline phosphatase

PO_4^{--} esters $\rightarrow$ PO_4^{--} ions

3 Pyrophosphate inhibitor

Function

Secrete

2 Osteo clasts

Bone eating cells

1 H^+ ions: dissolve crystals.

Mech. Ptn pump.

mem. H dependent ATPase

2 Acid protease: dissolves collagen

3 Osteo cytes: Function in exchange of Ca^{++} with ECF.

NB Bone remodelling 4% of compact 20% of trabecular bones/year
2 million " units in human skeleton (osteoclasts & osteoblasts)

Calcium homeostasis

control of plasma calcium

1 First line of defense maintains Ca at 7mg in absence of PTH

a Exchangeable amorphous calcium phosphate $CaHPO_4$. Endo
area of 1 acre supplies 5-10g of Ca^{++} in 70-140 min

b Mitochondria of liver & intest allow Ca to flow in or out

(30)

2 Second line of defense

Hormones 3

- Ca raising hormones: Parathormone = PTH = Parathrin
Active Vit D₃ = 1,25(OH)₂cholecalciferol = 1,25(OH)₂CC
- Ca lowering hormone: Thyrocalcitonin TCT

Parathormone PTH

Calcitonin CT

Chief cells of parathyroid Origin Parafollicular cells of thyroid

Polypeptide 84 aa

Structure

Polypeptide 32 aa.

Ca raising H. (Hypercalcemic)

Action

Ca⁺⁺ lowering H. (Hypocalcemic)

1 On bones

resorption. Osteolysis

a Rapid phase: min. to hours

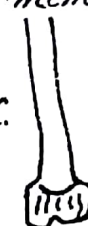
PTH binds to receptors of osteocytic mem.

- ++ Ca⁺⁺ permeability
- ++ Ca⁺⁺ pump to ECF
under effect 1,25(OH)₂CC.

b Slow phase days to weeks

PTH ++ IL-6 & RANKL (osteoblasts)

- stim. osteoclasts (no PTH recept)
- bone resorption (Discur)



Bone building hormone

a -- number & activity of osteo CLASTS

b ++ activity of osteo BLASTS & alkaline phosphatase.

2 On kidneys

reabsorption

a PC tubules: -- PO₄³⁻ reabsorp.
i.e. phosphaturic action

b DC tubules: ++ Ca⁺⁺ reabsorp.

c ++ formation of 1,25(OH)₂CC
via activation of 1α hydroxylase

d ++ Mg & H⁺ reabsorption



a -- PO₄³⁻ & Ca⁺⁺ reabsorption
i.e. ++ PO₄³⁻ & Ca⁺⁺ secretion

XB CT ≠ PTH on Ca⁺⁺
= PTH on PO₄³⁻

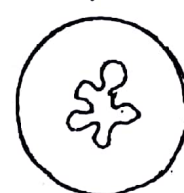
b -- 1α hydroxylase activity of proxim. convol. tubules.

3 On intestine

absorption

of Ca⁺⁺ via 1,25(OH)₂CC

Mech ++ Calbindin



RANKL Receptor Activated NF KB Ligand

Endo

Regulation of PTH secretion

PTH is not under ant. pituitary
PTH secretion is ++ by:

- 1 -- plasma Ca^{++} .
- 2 ++ " PO_4^{--} (due to -- Ca^{++}).
- 3 ++ cAMP e.g. β adrenergic stim.

PTH secretion is -- by:

- 1 ++ plasma Ca^{++}
- 2 ++ 1,25 $(OH)_2 D_3$.

Regulation of CT secretion

CT secretion is ++ by:

- 1 ++ plasma Ca^{++} .
- 2 β adrenergic agonists.
- 3 estrogen, prolactin & dopamine.
- 4 GIT hormones: gastrin & CCK
to prevent post prandial hypercalcaemia

CT secretion is -- by:

- 1 -- plasma Ca^{++} .

The collective functions of PTH:

Blood Hypercalcaemia & Hypophosphatemia.

Urine Hypocalciuria then hypercalciuria & Hyperphosphaturia

PTH receptors & mechanism of action of PTH

- 1 PTH / PTH rP (rP = related protein) in osteoBLASTS & osteoCYTES
- 2 PTH₂R in placenta, pancreas & brain

1 & 2 receptors are serpentine coupled to G_s & G_q (G proteins)

G_s activates adenylyl cyclase $\rightarrow$ ++ cAMP $\rightarrow$ activates protein kinase A

G_q " PLC $\rightarrow$ ++ intracell. Ca^{++} $\rightarrow$ activates protein kinase C

- 3 CPTH: C terminal of PTH molecule binds to it

N.B. PTH rP: (40 aa) has PTH action, also acts as growth factor for skin, hair, breast chondrocytes

1, 25 $(OH)_2 D_3$ = 1, 25 $(OH)_2 CC$ steroid hormone

Formation:

- In skin keratinocytes
7 dehydrocholesterol $\xrightarrow{\text{Ultraviolet}}$ previtamin $\xrightarrow[\text{3 days}]{\text{Infrared}}$ cholecalciferol (Vit. D₃)
- In liver $\xrightarrow[OH]{25}$ 25(OH) CC (stored) • In kidney $\xrightarrow[\alpha_1 \text{ hydroxylase}]{\text{PTH activates Prox. C. tubules}}$ 1, 25(OH)₂ CC

Mechanism of action: Genomic (steroid)

1, 25(OH)₂ CC binds to cytoplasmic receptors $\rightarrow$ transcribes mRNA

$\rightarrow$ Formation of Ca binding protein Calbindin D.

N.B. receptors mainly in intestine, kidney & bones.

But, also in ant. pit, skin, breast, muscles, lymphocytes & monocytes.

Endo (32)

Regulation of 1,25 DHCC:

-- plasma Ca^{++} $\rightarrow$ ++ PTH.

Both -- Ca^{++} & ++ PTH converts $25(\text{OH})\text{CC}$ $\xrightarrow{1\alpha\text{ hydroxylase}}$ $1,25(\text{OH})_2\text{CC}$
 ++ $1,25(\text{OH})_2\text{CC}$ feeds back:

- negatively on $1\alpha\text{ hydroxylase}$ $\rightarrow$ -- $1,25(\text{OH})_2\text{CC}$.
- positively on another enzyme $\rightarrow$ ++ $24,25(\text{OH})_2\text{CC}$.

Physiological actions of 1,25 DHCC:

- 1 Intestine ++ calbindin D $\rightarrow$ ++ Ca^{++} absorption for weeks
- 2 Kidney ++ calbindin D $\rightarrow$ ++ Ca^{++} reabsorption in DC tubules
 ++ PO_4^{--} " in Proximal "
- 3 Bones • If Ca^{++} , PO_4^{--} are high, it stim. osteoblastic activity
 • If Ca^{++} , PO_4^{--} are low, it stim. osteoclastic activity

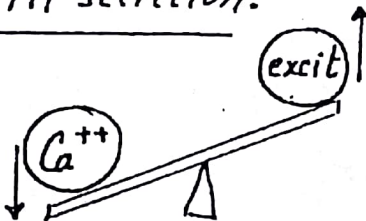
Note 1,25 DHCC ++ ATPase ++ ALP

Disturbance of parathyroid gland

- 1 Hypoparathyroidism usually faulty removal during thyroidectomy.
 $\rightarrow$ -- plasma Ca^{++} $\rightarrow$ ++ neuromuscular excit. (tetany)
- 2 Hyperparathyroidism
 - a prim. due to tumours in parathyroid $\rightarrow$ ++ Ca^{++} $\rightarrow$ -- excitability
 - b secondary due to chronic renal diseases $\rightarrow$ ++ PO_4^{--} (retention)
 $\rightarrow$ -- plasma Ca^{++} $\rightarrow$ ++ PTH secretion.

Tetany

- Definition: ++ neuromuscular excitability due to -- ionised calcium in plasma
- Mechanism -- Ca^{++} $\rightarrow$ -- threshold of activation of voltage gated sodium channels $\rightarrow$ slight stim. of nerves or even spontaneously $\rightarrow$ train of nerve impulses $\rightarrow$ spasmodic muscle contraction



• Causes

- 1 Hypoparathyroidism.
- 2 -- Ca^{++} a intake > needs mainly infants & pregnant ♀
 b absorption due to -- Vit D₃ or alkalinity of intestine
- 3 Alkalosis $\rightarrow$ -- solubility product $\rightarrow$ -- ionised (not total) Ca^{++}
- 4 Phosphate retention in advanced renal diseases.

• Types of tetany :

① Latent (Hidden) tetany : No manifestations during rest
Diagnosis : plasma calcium below (9.4) but above 7 mg%.

2 Provocation tests



a) Chvostek sign Tapping facial nerve in front of ear.
Normal : only feeling of a tap.
Tetany : + involuntary reflex twitching of ipsilateral facial muscles.



b) Trousseau sign or accoucheur hand Occlusion of circulation of arm for few minutes with BP cuff above systolic blood pressure.
Normal : feeling of ischemic pain in the upper limb.
Tetany : + carpal spasm i.e. flexion of wrist & metacarpophal. extension of all interphalangeal joints & adduction of thumb.

c) Erb sign Application of galvanic electric current to the medial side of forearm.
Normal : Cont. of ul. limb ms only at the make & break of current.
Tetany : Involuntary reflex carpal spasm during the whole period of current flow.

② Manifest tetany : Manifestations appear during rest.
Fibrillary twitches, then clonic, then tetanic contraction in the form of carpopedal spasm, laryngeal & respiratory spasm which may lead to cyanosis, asphyxia & death.
Plasma calcium below (7 mg/dl).

• Treatment of tetany :

① Manifest tetany Immediate injection of Ca gluconate 10ml 10% Intravenously slowly (to avoid Ca rigor of heart).

② Latent tetany & in between attacks of manifest tetany

a. Diet rich in calcium.

b. Vitamin D injection to help absorption.

c. Acidifying salts to help ionisation of Ca^{++} .

③ Treatment of the cause : e.g. alkalosis or renal failure.

Endo

Adrenal glands

- Adrenal glands are essential for life. It consists of:
 - 1 Adrenal medulla 20% not essential for life.
It secretes catecholamines (epinephrine, norepinephrine & dopamine).
 - 2 Adrenal cortex 80% essential for life (a & b)
 - a Zona Glomerulosa secretes mineralocorticoids
It maintains Na^+ & K^+ balance and ECF volume.
 - b Zona Fasciculata secretes mainly glucocorticoids
It regulates CHO, fat and ptn metabolism.
 - c Zona Reticularis secretes mainly sex hormones
It contributes in establishing & maintaining of second sex characters.

● Synthesis of adrenocortical hormones :

Adrenocortical hormones are STEROID formed from cholesterol :

- a from plasma transported to adrenal cells by endocytosis.
- b from the cortical cells from acetylcoenzyme A (small amount)
Under ACTH stim., the b source becomes the most import. source.

GLUCOCORTICOIDS

They are formed in Z. Fasciculata (mainly) & also in Z. reticularis.

- Cortisol (hydrocortisone) 95% & corticosterone 4%.

● Synthesis of glucocorticoids :

- 1 In storage vacuoles: Cholesterol ester $\xrightarrow{\text{Hydrolysed}}$ Free cholesterol.
- 2 In mitochondria: Free cholesterol $\xrightarrow{\text{inner mem.}}$ Pregnenolone.
- 3 In E. Reticulum: Pregnenolone $\longrightarrow$ 11 deoxycortisol.
- 4 In mitochondria: 11 deoxycortisol $\xrightarrow[\text{11 position}]{\text{Hydroxylated}}$ Cortisol

Note Cortisol is not stored in appreciable amount in cortical cells

- Transport of glucocorticoids

- 1 75% bound to a corticosteroid binding globulin (CBG) = transcortin.
- 2 15% bound to albumin.
- 3 10% Free (Active form).

CBG formation in LIVER ++ by estrogen (pregnancy).
-- in hepatic cirrhosis & nephrosis.

- Metabolism and excretion of glucocorticoids

In Liver: Most cortisol is reduced & conjugated to glucuronic acid and excreted in urine. Hepatic inactivation -- in liver diseases, surgery and stresses → marked ++ in free cortisol.

- Actions of Glucocorticoids Cortisol is essential for life.

3 types of actions depending on cortisol plasma level.

i.e. Permissive (low level) Physiological (normal) Pharmacological (high)

Permissive actions i.e. in small amounts, cortisol allows but doesn't share in certain hormone actions

- 1 Glycogenolysis: produced by glucagon.
- 2 Lipolysis: " by catecholamines and GH.
- 3 VC of arterioles: " by " and angiotensin II

Physiological actions i.e. produced by normal plasma level: 9

- ① Effect on metabolism ++ mobilization of fuel.

☑ CHO

Diabetogenic

- ① ++ GLUCONEOGENESIS by the liver.

Mech. 1 ++ extrahepatic ptn catabolism (in muscles and lymphoid tissues) → ++ aa in blood.

2 ++ hepatic uptake of aa & conversion to glucose;

a ++ hepatic glucose release

b ++ " gluconeogenesis

③ End

- ② -- glucose utilization by muscle and adipose tissue.
 & lowers their sensitivity to insulin Anti-insulin action
 a -- affinity of insulin receptors to insulin.
 b -- mobility of glucose transporter.
 c -- phosphorylation.
Note Brain & heart are spared from the anti-insulin action.

[B] Ptn : Extrahepatic catabolism.

- 1 -- ptn stores in ALL cells except LIVER cell.
 -- ptn synthesis & ++ ptn catabolism
- 2 -- aa transport into ms & adipose tissues → ++ plasma aa
- 3 ++ aa transport into liver cells

[C] FAT : Lipolysis

- 1 ++ activity of hormone sensitive LIPASE in adipose tissue.
 Triglycerides breaks → glycerol & FFA (source of energy in stress)
- 2 If insulin -- e.g DM, ++ ketone bodies i.e ketogenic

② In stress : Antistress

Physical & mental stresses ++ ACTH → ++ Cortisol in blood.

Importance Permissive action for pressor & lipolytic effect of catecholamines
 ++ blood glucose & FFA i.e energy sources
 ++ blood aa i.e formation of ptns by damaged tissues

③ On appetite : Normally, 2 opposing equivocal effects

- a ++ appetite by ++ neuropeptide Y in hypoth. & CRH (anorexogenic)
- b -- appetite by ++ leptin by adipocytes.

④ On CVS Maintenance of normal ABP

- a inotropic action ++ β receptors & Na-K ATPase on heart.
- b -- vasodilator prostaglandins.
- c maintains bl. volume; by -- permeability of vascular endothelium

End (37)

⑤ On blood cells:

a ++ number of RBCs, platelets and neutrophils

However, it depresses function of neutrophils.

b -- eosinophils (++ apoptosis & sequestration in spleen & lungs)
-- T lymphocytes (-- lymphocyte mitosis)

⑥ On CNS :

a It modulates excitability, behaviour & mood of individuals.

b -- REM sleep & ++ slow wave sleep & time spent awake.

⑦ On skeletal muscles :

++ Acetylcholine → ++ N-M transmission & contraction.

⑧ On kidney :

a In H_2O Load : rapid excretion

In Acid Load : glutamate → α ammonium ions (fight acidosis)

b ++ glomerular plasma flow, and in turn, ++ GFR

d -- PO_4 reabsorp. in Proximal tubules → ++ $PO_4^{=}$ excretion

⑨ Other effects :

a very slight MINERALOCORTICOIDS activity

b During fetal life : maturation of surfactant in lungs

Pharmacological actions high plasma level (therapy or tumour) 5

① On bone : Osteoporosis

a -- bone formation • -- active osteoblasts.

• -- synthesis of type I collagen (main bone matrix)

• Antivit. D action i.e -- absorp & reabsorp of Ca^{++} & $PO_4^{=}$

b ++ bone resorption.

② On connective tissue :

a -- collagen synthesis → thinning of skin & capillaries (fragile)
→ capill. rupture & cutaneous hge.

End (38)

b -- proliferation & function of fibroblasts.

Note a & b antagonise growth of children under cortisol ttt.

③ Anti inflammatory :

a cortisol stabilises the wall of lysosomes.

b -- synthesis, secretion & actions of $IL-1$ & 50 , cortisol blocks early stages of inflamm. and promotes rapid resolution of inflam.

④ Anti allergic :

Cortisol prevents histamine release & blocks leukotrienes formation.

„ doesn't prevent antigen-antibody reaction.

„ is used in ttt of asthma, delayed hypersensitivity reactions...etc.

⑤ Immunity and lymphoid tissue :

a -- humoral immunity -- production & level of immunoglobulins

b -- cellular immunity -- $IL-2$ „ & -- T lymphocytes

c -- interferon production (-- destruction of tumour cells & viruses)

Advantage prevention of rejection of transplanted tissues

Disadvantage Fulminating infections e.g TB & tumorigenic

● Control of Glucocorticoid secretion

① Hypothalamus CRH

In stresses, hypoth ++ CRH secretion $\rightarrow$ ++ ACTH $\rightarrow$ ++ cortisol

② Ant. pituitary ACTH

- ACTH ++ number, size & activity of cortical cells.

- ACTH acts via cAMP & Gs to convert cholesterol esters to free cholesterol via ptn kinase A.

- ACTH is not an important regulator of aldosterone secretion

- ACTH has MSH activity (ACTH has the same number of aa)

③ Free cortisol -ve feedback

End (39)

- ++ Free cortisol -ve feedback → -- ACTH (ant pit) & -- CRH (hypoth)
- ④ Circadian rhythm related to cycles of stress i.e neuronal CRH & intern ACTH & cortisol ++ in early morning & lowest at evening
- ⑤ Large doses of vasopressin, serotonin & VIP act directly on the adrenal cortex to stimulate cortisol production

Mineralocorticoids

ALDOSTERONE 90% Desoxycorticosterone $\frac{1}{50}$ potency of aldosterone.
Corticosterone has slight & Cortisol very slight mineralocorticoid activity

• Transport :

60% is bound to transcortin & albumin.

Binding is weaker than for cortisol → shorter $\frac{1}{2}$ life 20-30 min.

• Metabolism : 90% is cleared by the liver in a single passage. i.e reduced and conjugated with glucuronic acid & excreted in urine

• Action of Aldosterone :

Aldosterone maintains ECFV by conserving body sodium.

① On kidney Distal & collecting tubules

a P cells ++ exchange transport of Na^+ and K^+

① ++ reabsorption of Na^+

Aldosterone - Receptor complex induces DNA to form different types of mRNA which, in turn, in 30 min ++ ptn synthesis in ribosome to ++ reabsorp of Na^+ in 45 min

a At luminal border : ++ Na channel proteins

→ ++ Na diffusion i.e passive reabsorption

b At basolateral border : ++ Na^+ -K ATPase

→ ++ energy production ++ Active Na reab

H_2O is passively reabsorbed with Na^+ . End ④

So, ECF volume expands in an isotonic manner

② ++ K secretion.

Rate of Na^+ reabsorption begins to increase after 45 minutes and reaches its effect after several hours i.e. slow action.

⑥ Intercalated (I) cells

++ H secretion by ++ activity of H^+ ATPase proton pump.

→ mild alkalosis & increased urine acidity

② On colon, sweat, salivary & gastric glands ++ Na^+ reabsorp & ++ K^+ secretion

● Control of aldosterone secretion : 4

① Plasma K^+ level

++ K^+ level by 1 mEq/L e.g. after meal → ++ aldosterone.

Mech: ++ conversion of cholesterol to pregnenolone.

& corticosterone to aldosterone.

Depolarizing adrenal cells open voltage gated Ca^{++} channels

→ ++ intracellular Ca^{++}

② Activation of the renin-angiotensin system

Angiotensinogen $\xrightarrow{\text{Renin}}$ Angiotensin I $\xrightarrow{\text{ACE}}$ Angiotensin II

Angiotensin II has the following effects (A II) :

a A II binds to receptors on Z. granulosa cell → ++ Aldosterone ^{synthesis} secretion

b Early: cholesterol → pregnenolone Late corticosterone → aldosterone

c Hypertrophy of Z. glomerulosa cells.

Atrial natriuretic peptide (ANP) : -- renin secretion and

-- response of Z. glomerulosa to A II → -- aldosterone.

Renin secretion is increased by : (-- renal bl. flow and pressure)

1 -- ECF volume e.g. hge 2 Narrowing of renal artery

3 -- body Na^+ (dietary restriction or acute diuresis)

4 Assuming an upright posture for several hours

5 Increased sympathetic activity (hypovolemia) or catecholamines acting on β adrenergic receptors

End (41)

③ Plasma Na^+ level

-- plasma Na^+ of 20 mEq/L (acute or slow) ++ aldosterone.

Mechanism Initially, -- Na in renal tubules is sensed by macula densa $\rightarrow$ ++ aldosterone secretion

Secondly -- ECF vol via renin angiotensin system.

④ ACTH is not important regulator of aldosterone secretion.
It has a tonic role -- ACTH -- Z. glomerulosa response to stimuli

Action of Adrenal Androgen and Estrogens

● Adrenal androgens: DHEA & Androstenedione.

- They are under ACTH (not gonadotropins) control.

- Their function is due to peripheral conversion to potent testosterone.

- ♀ : maintain pubic & axillary hair & stimulate RBCs production

♂ : their effects are masked by testicular androgens (greater amount)

● Adrenal estrogens :

- Secreted directly or from conversion of adrenal androgens to estrogens.

- Source of estrogen in both men & postmenopausal women.

Disorders of adrenal cortex : Hyper or Hyposecretion

① Hypersecretion of mineralocorticoids 3

A. Primary hyperaldosteronism (Conn's syndrome)

Cause Aldosterone secreting tumours of adrenal cortex

Features :

1 Hypokalemia results in

a Hypokalemic nephropathy no concent. ability $\rightarrow$ polyuria

b Muscle weakness due to hyperpolarization.

c -- glucose tolerance due to -- insulin secretion

2 H^+ loss $\rightarrow$ Metabolic alkalosis $\rightarrow$ Tetany (42)^{End}

- 3 Hypernatremia $\rightarrow$ ++ ECF volume & hypertension
However, no edema i.e. Escape phenomenon due to:
Increased secretion of ANP (due to ++ CVP).
- ANP -- Z. glomerular response to stimuli.
- ANP -- renin secretion $\rightarrow$ -- Angiotensin II.
- ANP has actions opposite to angiotensin II & aldosterone.

[B] Secondary hyperaldosteronism.

Secondary to heart failure, liver cirrhosis or nephrosis $\rightarrow$ ++ renin & A II
There is marked edema i.e. no escape phenomenon. but other effects
Slight ++ in plasma Na^+ $\rightarrow$ ++ ECF vol and hypertension

[C] Glucocorticoids - remediable aldosteronism.

Cause A genetic error reduces a hybrid gene $\rightarrow$ ++ sensitivity
of Z. glomerular to ACTH $\rightarrow$ ++ aldosterone secretion
ttt Glucocorticoids that suppress ACTH secretion.

(2) Cushing's syndrome

Causes :

- 1 Adrenocortical tumours that mainly secrete cortisol
i.e. ACTH independent. ACTH is decreased by -ve feedback
- 2 Secondary to pituitary tumour that secretes ACTH
i.e. ACTH dependent. ACTH is increased.
- 3 Administration of large amount of cortisone (therapy)

Features :

[1] Glucocorticoid effects

a Excess protein catabolism

- Skin thin, poor wound healing, capillaries are fragile $\rightarrow$ bruises. Hair is thin.
- Muscles Atrophy & weakness

End

- Bones Osteoporosis → Fractures of bones

; due to -- bone formation & ++ bone resorption.

X.B -- phn synthesis of lymphoid t. → -- immunity & ++ infections

b Fat metabolism

1 Trunkal obesity : Moon face and Buffalo hump.

2 Purple striae : bl. vs are seen under the thin stretched skin

3 Hyperlipemia & ketosis : associated with diabetes

c CHO metabolism

1 Hyperglycemia (++ gluconeogenesis & -- glucose utilization)

2 Insulin-resistant diabetes mellitus in a predisposed pt.

d CNS Accelerates basic EEG rhythm, increased appetite, insomnia and euphoria

[2] Mineralocorticoids → Hypertension in 85% of pt. caused also by ++ AI and a direct effect of cortisol on arterioles

[3] Androgen excess Hirsutism i.e ++ facial hair and acne

[4] ACTH excess (in ACTH dependent) → Pigmentation

③ Hypersecretion of Adrenal Androgen Adrenogenital Syndrome
Effects depend on age and sex.

[a] During intrauterine life : Female pseudohermaphrodite.

The baby has the Gonads (ovaries) & Genetic constitution (XX) of one sex (♀) and the Genitalia of the opposite sex (♂)

[b] In the prepubertal male Male precocious pseudopuberty.

Early appearance of secondary Sex characters; but no testicular growth.

[c] In adult females Female adreno-genital syndrome

i.e Masculinization

beard, deep voice, acne & may be baldness
or distribution of hair and fat.
++ muscle bulk

Atrophy of uterus, amenorrhoea, atrophy of breast.
Enlargement of clitoris

End (44)

17 ketosteroids in urine ++ in all cases of ++ adrenal androgen.

Hyposecretion of adrenal cortex Addison's syndrome

Causes Destruction of adrenal cortex by autoimmune disease, tuberculosis or cancer.
N.B total destruction is fatal.

Effects

① Cortisol deficiency :

- a Hypoglycemia -- Fasting bl. glucose (due to -- gluconeogenesis) & post-prandial hypoglycemia (due to ++ insulin sensitivity).
- b Lack of energy substrate → severe muscle weakness, fatigue, loss of weight and anorexia.
- c Pigmentation (gums, p areas & nipple) due to ++ ACTH (due to -- cortisol)
- d -- resistance to stresses.
- e ++ eosinophils and lymphocytes and -- neutrophils.

② Aldosterone deficiency :

- a Hyponatremia → -- ECF vol, dehydration & hypotension in 100% Pt dies in shock if not treated.
Diarrhoea & polyuria due to ++ loss of Na^+ , Cl^- and H_2O .
- b Hyperkalemia → cardiac arrhythmia & weakness of cardiac contract
- c H^+ retention → mild metabolic acidosis

③ Adrenal androgen deficiency :

- a Loss of pubic and axillary hair in females
- b Anemia

Addisonian Crisis

Addisonian Pt fails to respond to stress by ++ glucocorticoids

→ collapse, shock, hyperkalemia and hypoglycemia
Emergency ttt : IV cortisol & isotonic NaCl infusion. End

Adrenal medulla

It is modified sympathetic ganglion.

norepinephrine $\xrightarrow[\text{(PNMT) in adrenal medullary cells}]{\text{Phenyl ethanol N-methyl transferase}}$ epinephrine

- Storage : In granulated vesicles, bound to ATP & chromogranin A (pn).
- Release : A. potential releases Acetylcholine which opens Ca channel. Ca^{++} triggers exocytosis of catecholamines, ATP & chromogranin A.
- Actions of epinephrine and norepinephrine

① CVS :

(a) Heart : Both hormones ++ force, rate & excitability of heart viz β_1

(b) Bl. vs :

- Norepinephrine : VC of almost all organs viz $\alpha_1 \rightarrow ++ \text{TPR}$

- Epinephrine : VD of sk ms & liver via β_2 receptors
VC of other sites $\rightarrow -- \text{TPR}$

(c) ABP, HR & CO :

- Norepinephrine : ++ systolic & diastolic BP reflex $\rightarrow -- \text{HR}$
direct effect on heart (++HR). So, CO is decreased.

- Epinephrine : ++ (widening) of PP $\rightarrow -- \text{HR}$ (direct effect on heart (++HR))
So, CO is increased.

② CNS :

a Both : ++ alertness due to activation of reticular formation.

b Epinephrine : anxiety and fear

③ Metabolism :

(a) On blood glucose

- activate hepatic phosphorylase via β & α $\xrightarrow{(\text{cAMP})(\text{Ca}^{++})}$ glycogenolysis $\rightarrow ++ \text{bl. glucose}$.
- activate muscle phosphorylase via β & α $\xrightarrow{\text{G6P}}$ pyruvate $\rightarrow$ lactate diffuses to blood & is converted in liver to glycogen
- Catecholamines via β receptors ++ insulin & glucagon secretion

The net effect -- insulin $\nearrow$ ++ glucagon $\rightarrow$ ++ bl. glucose
4 Epinephrine -- peripheral utilization of glucose.

(b) On adipose tissue

Epinephrine: Lipolysis viz hormone sensitive lipase $\rightarrow$ ++ FFA

(c) On metabolic rate (MR) MR increases viz

- -- Heat loss: cutaneous VC which -- heat loss

- ++ Heat gain: ++ muscle tone $\nearrow$ ++ hepatic oxid of lactate.

(d) On plasma K^+



- initial rise in plasma K^+ due to a release of hepatic K^+

- Followed by prolonged fall due to influx of K^+ in sk. muscle

● Regulation of adrenal medullary secretion:

Catecholamine secretion is low in basal states $\nearrow$ -- more during sleep.

Increased secretion is part of diffuse sympathetic discharge caused by:

1 Emergency situations:

2 Stressful stimuli viz action on hypothalamus. e.g

(a) Hypo thermia $\nearrow$ cold: Catecholamines have calorogenic action

(b) Hypo glycemia : " ++ bl. glucose

(c) Hypo tension $\nearrow$ hge: " produce VC.

The pressor effect requires the presence of glucocorticoids

● Adrenal medullary tumour Pheochromocytomas

- Most types secrete norepinephrine

$\rightarrow$ episodic or sustained hypertension.

- Some types secrete epinephrine

$\rightarrow$ hyperglycemia, glycosuria $\nearrow$ elevated metabolic rate.

End

(47)

Pancreas

Islets of Langerhans

<u>Type of cells</u>	<u>4 hormones</u>	
	<u>% of total</u>	<u>Secrete</u>
1 α (A) cells	25 %	Glucagon
2 β (B) cells (centre)	60 %	Insulin
3 δ (D) cells	10 %	Somatostatin
4 (F) cells	5 %	Panc polypeptide

INSULIN

- Structure : Polypeptide (2 chains A & B) linked by disulfide bridge.
There is minor difference in aa in insulin of different species
- Synthesis :
 - In ribosomes Pre-pro insulin (4) peptides in sequence.
Signal, B chain, a connecting (C peptide) and A chain.
 - In endoplasmic reticulum Pro insulin (3) peptides
i.e. splitting of signal peptide
 - In Golgi complex Insulin (2) peptides (A & B chains)
- Secretion : By exocytosis which needs Ca^{++} .
Granules move via microtubules to cell membrane releasing:
 - 90-97% as insulin and equimolar amount of C peptide.
 - Rest as proinsulin with little biological activity.
- Mechanism of insulin release :
Glucose enters β cells via glucose transporter GLUT2
generating $\rightarrow$ ATP that closes ATP sensitive K^+ channels
 $\rightarrow$ K^+ efflux $\rightarrow$ Depol. $\rightarrow$ opens voltage gated Ca^{++} chann
 $\rightarrow$ influx of Ca^{++} to β cells $\rightarrow$ activates Ca dependent
kinase that triggers insulin release by Exocytosis End.

- Insulin circulates FREE in plasma (Half life 5 min)
- Insulin binds to its receptor is internalised by receptor mediated endocytosis & is destroyed by insulinase in liver, kidney & other tissues
- Normally, little or no insulin passes in urine
- Insulin like substances in blood :
 - IGF_I & IGF_{II} polypeptides formed in liver & other tissues
 - Not suppressed by insulin antibodies
 - Large amount bound to ptn of high MW, small amount are free
 - Insulin like activity is weak compared to that of insulin.

- Insulin receptors :
 - Membrane receptors made of 4 subunits held by disulfide link
 - Insulin binds to 2 α subunits (outside) & triggers activation of tyrosine kinase of the 2 β subunits (inside) producing :
 - autophosphorylation of the β subunit that results in
 - phosphorylation & dephosphorylation of insulin receptor substrates IRS₁, IRS₂, IRS₃ & IRS₄

NB Insulin receptors are found also in cells in which insulin does not increase glucose uptake.

Number of R $\left\{ \begin{array}{l} \text{++ in starvation} \\ \text{-- in acromegaly} \\ \text{ie ++ GH} \end{array} \right.$ Affinity $\left\{ \begin{array}{l} \text{++ starvation} \\ \text{adrenal hypofunct} \\ \text{-- by excess cortisol} \end{array} \right.$

- Cellular effects of insulin on mem, cytoplasm and nucleus
 - [a] Rapid (seconds) : ++ permeability of insulin sensitive cells (muscle, adipose cells & liver) to glucose due to shift of glucose transporters from cytoplasm to cell membrane. Also ++ permeability to aa, K⁺ & PO₄²⁻ End (49)
 - [b] Intermediate (minutes) Phosphorylation & dephosphorylation of enzymes

☐ delayed (hours) change in rate of formation of mRNA & DNA

- Glucose transporters

- 1 Secondary active transport: Na^+ glucose cotransport
 SGLT_1 & SGLT_2 in intestine & renal tubules
- 2 Facilitated diffusion: 7 glucose transporters ($\text{GLUT}_1 - \text{GLUT}_7$)
 GLUT_4 is the only one sensitive to insulin (in muscles & adipose t.)

It is present in vesicles in the cytoplasm.

Insulin causes the $\rightarrow$ to move & fuse with the cell membrane
via phosphoinositide 3 kinase

Other glucose transporters (not insulin sensitive) stay at cell membrane
Exercise, independent of insulin, moves GLUT_4 vesicles to cell mem.
via 5 AMP activated kinase $\rightarrow$ blood sugar.

- Insulin stimulates glucose uptake

- 1 In muscle & adipose t. Insulin $\rightarrow$ glucose entry via $\rightarrow$ GLUT_4
- 2 In liver cells. Insulin $\rightarrow$ glucose entry via glucokinase enzyme
 $\rightarrow$ $\rightarrow$ glucose phosphorylation $\rightarrow$ glucose conc inside liver cells
In other tissues e.g. brain, kidney, intestine, insulin doesn't $\rightarrow$ glucose uptake which occurs via $\text{GLUT}_1, 2, 3$ & 5 or SGLT_1 & SGLT_2

- Relation of insulin to potassium

Insulin $\rightarrow$ K^+ entry to cells by $\rightarrow$ activity of $\text{Na}^+ - \text{K}^+ \text{ATPase}$.
So, hyperkalemia e.g. in renal failure is treated by insulin & glucose
Again, hypokalemia e.g. in hyperaldosteronism $\rightarrow$ insulin secretion
 $\rightarrow$ diabetic glucose tolerance curve & DM becomes worse.

Also, thiazide diuretics that $\rightarrow$ K^+ produce the same effects

- Metabolic actions of insulin:

① CHO

hypoglycemia

End

50

A) On muscles

Following a meal, insulin $++$ transport of glucose into the muscle cells via GLUT₄ (Muscles 50% of body mass)
→ most of the lowering of bl. glucose after insulin release.

- 20-50% of glucose that enters the ms is oxidised.
- Rest is stored as glycogen (insulin stim. glycogen synthetase).

B) On adipose tissue

Insulin stimulates glucose entry into fat cells via $++$ GLUT₄
• Glucose forms glycerol + fatty acids → triglycerides

C) On liver

Insulin stimulate glucose entry via $++$ activity of glucokinase

N.B Liver cells utilize GLUT₂ (insulin insensitive)

Insulin promotes glycogenesis via glycogen synthetase

„ inhibits glycogenolysis and gluconeogenesis.

② On fat

Lipogenesis

A) On liver Excess glucose insulin → FFAs → triglycerides in VLDL which are transported in blood to adipose tissue

B) On adipose tissues Insulin promotes lipogenesis

Insulin $++$ glucose transport → glycerol + FFA → triglycerides

C) Inhibition of lipolysis via $--$ of hormone sensitive lipase

Insulin is the major antiketogenic hormone.

It $--$ ketone body formation $++$ use of ketoacids by tissues

③ On Ptn

Anabolic

1 $++$ transport of aa. 2 $++$ mRNA. 3 $++$ DNA.

4 Ptn sparing via $--$ of gluconeogenesis 5 $--$ ptn catabolism.

④ On Growth

mainly cartilage, bone and muscles

Gene of insulin & its receptor are related to genes of IGF₁ & IGF_{II}

Insulin $++$ transcription of related gene of IGF₁ End (51)

● Control of insulin secretion

Blood nutrients

- 1 Glucose level : Glucose is the most important stimulant for insulin
++ bl. glucose $\rightarrow$ ++ insulin secretion
Insulin secretion is maximal at bl. glucose 300 mg%

- 2 Amino acid level

Some aa (e.g. arginine and lysine) ++ insulin secretion.
Amino acids potentiate the glucose stimulus for insulin.

Hormones

- 3 Gastro-intestinal hormones

Oral glucose > IV glucose for insulin release due to secretion of GLP, glucagon like polypeptide 1 (GLP₁), gastrin, secretin, etc.

- 4 Islet hormones

a Insulin has a -ve feedback effect on its own secretion

b Glucagon ++ insulin secretion.

c Somatostatin -- insulin secretion

- 5 Other hormones Cortisol, GH, thyroid hormones, estrogen, progesterone & placental lactogen ++ insulin secretion
Prolonged secretion of one of these hormones in large amount $\rightarrow$ exhaustion of β cells $\rightarrow$ DM

Leptin released from adipocytes -- insulin secretion

Neurogenic

- 6 Autonomic nerves Vagus ++ insulin secretion via M_4 receptors coupled via G protein to phospholipase C $\rightarrow$ ++ $IP_3 \rightarrow$ ++ Ca^{++}

Sympathetic -- insulin secretion via α_2 receptors

N.B. autonomic nerves maintain islet sensitivity to glucose

- 7 Catecholamines α receptors -- insulin > β receptors ++ insulin
- 8 cAMP β stimulants, glucagon, GLP $\rightarrow$ ++ cAMP $\xrightarrow{\text{via cAMP}}$ ++ insulin

GLUCAGON

Hyperglycemic hormone

- Structure : Polypeptide.
- Origin : α cells of islets and upper GIT
- Synthesis : As preproglucagon in α cells and L cells of lower GIT and in the brain (MW 3500 29 aa)
- Actions of glucagon :

1 On CHO

Hyperglycemia

Injection of $1 \mu\text{g/Kg}$ body weight $\rightarrow$ bl glucose 20 mg/dl in 20 min
via Glycogenolysis & Gluconeogenesis in liver.

Mechanism Glucagon binds to 2 types of receptors
 $\rightarrow$ $\uparrow$ cAMP (via adenyl cyclase) & $\uparrow$ Ca^{++} (via phospholipase C)

2 On Ptn

$\uparrow$ aa uptake by liver cells & gluconeogenesis

3 On Fat

Lipolysis & Ketogenesis

It inhibits triglyceride storage in liver

④ Calorigenic i.e. $\uparrow$ metabolic rate due to gluconeogenesis.

⑤ On heart large dose $\rightarrow$ +ve inotropic via cAMP.

⑥ $\uparrow$ secretion of GH, insulin and pancreatic somatostatin.

- Regulation of glucagon secretion :

Glucagon secretion is increased by :

decreased by :

1 -- bl. glucose 3rd day of starvation
i.e. time of maximal gluconeogenesis

1 Glucose,
FFA & ketones

2 $\uparrow$ bl. aa after meal
especially gluconeogenic a.a.

3 GI hormones CCK & gastrin
i.e. Hormones $\uparrow$ by aa (ptn meals)

2 Secretin

3 Somatostatin

Symp. n.s. stimulation

4 β adrenergic stim. via cAMP

4 Insulin (53)
5 α adrenergic stim.

5 Heavy exercise

6 Stressful stimuli & infection

N.B. Vagal stim. ++ glucagon

6 GABA : released from

B cells by hyperglycemia
via GABA_A recept. & Cl⁻ channels

Somatostatin D cells of pancreas, GIT & hypothalamus

Action : Universal inhibitor

Main function is to prevent rapid exhaustion of food in between meals

1 Paracrine action : -- insulin, glucagon & panc polypeptide secretion

2 -- motility, secretion and absorption from GIT

Regulation of secretion : Ingestion of food ++ somatostatin

1 ++ blood glucose, aa and fatty acids.

2 GI hormones e.g. CCK.

NB Somatostatin is secreted from pancreas, hypoth. & GI mucosa

Glucose homeostasis i.e. regulation of bl. glucose.

● Fasting venous blood glucose 80-90 mg %

1 hour after meal 120-140 mg 2-3 hours after meal > i.e. normal

● Importance of glucose homeostasis :

- Hypo glycemia : dangerous ; Glucose is only fuel used by brain & retina

- Hyper glycemia : harmful → infection.

● Glucostatic mechanism LIVER & HORMONES

① Liver

a During absorption 2/3 of absorbed glucose is stored as glycogen.

Excess glucose is stored as fat (page 51)

b Post absorptive state liver prevents fall in bl. glucose by:

Glycogenolysis and Gluconeogenesis.

Glucose formed by gluconeogenesis is used by brain and not muscle & peripheral t. (no insulin). (54) End

(2) Hormonal mechanisms

a Insulin & glucagon act as feedback control system.

Hyperglycemia $\rightarrow$ ++ insulin $\rightarrow$ -- bl glucose

Hypoglycemia $\rightarrow$ ++ glucagon $\rightarrow$ ++ bl glucose e.g. exercise
e.g. starvation & exercise.

b In SEVERE hypoglycemia: Epinephrine (rapid action)

Mech -- bl glucose via hypoth $\rightarrow$ ++ " $\rightarrow$ Glycogenolysis

c In PROLONGED hypoglycemia: GH & Cortisol (hours to days)

Both -- glucose utilization & ++ fat utilization in most cells

Growth hormone	Cortisol
<u>Glycogenolysis</u> , <u>lipolysis</u> & <u>ketogenesis</u>	<u>Gluconeogenesis</u> , <u>lipolysis</u> & <u>ketogenesis</u>
-- <u>number</u> of insulin receptors	-- <u>affinity</u> of insulin to its receptors
-- glucose utilization by peripheral tissues	-- <u>glucose utilization</u> by peripheral tissues permissive Glucose utilization by tissues

Diabetes Mellitus DM

- Cause: Relative or absolute insulin deficiency
- Predisposing factors: - Hereditary - Obesity (--- number of insulin R)
Defect in insulin R or molecule, IRS, GLUT₄ or glucokinase.
- In animals insulin deficiency can be produced by:

- 1 Alloxan destroys β cells of islets
- 2 Drugs inhibit insulin secretion
- 3 Anti-insulin antibodies
- 4 Pancreatectomy.

• Types (forms) of DM

2 types

- [1] Type 1 Insulin Dependent DM (T1DM) 10%

Before 20 years Autoimmune: Ab destroy β cells

- [2] Type 2 Non Insulin Dependent DM (T2DM) 90%

- After 20 years usually obese Pt most common DM.

- Causes 1 insulin resistance $\rightarrow$ ++ insulin $\rightarrow$ β cells exhaustion

2 Genetic defect IRS-1 GLUT₄

- [3] Other forms: gestational, drug induced & secondary diabetes mellitus Endo
Glucokinase in β cells Insulin R. Insulin molecule
Manifestations related to insulin lack

(1) CHO Hyperglycemia results in

- Glycosuria $\rightarrow$ polyuria $\rightarrow$ polydipsia
- ++ OP of blood $\rightarrow$ cellular dehydration (also by polyuria)
- Polyphagia mech. Satiety centre fails to use glucose (no insulin)
- ++ loss of K^+ and Na^+ in urine.
- ++ Glucose $\rightarrow$ small amount of Hb A is not glycosylated to HbA_{1c}

② FAT Excessive utilization of fat. results in.

- ++ lipolysis $\rightarrow$ ++ plasma FFAs more than double.
- FFA $\rightarrow$ acetyl CoA & ketone bodies i.e ketosis
- ++ triglycerides (— lipoprotein lipase) ++ cholesterol, VLDL & LDL

③ Protein ++ Catabolism and — Synthesis

- loss of body weight — lack of energy i.e asthenia
- ++ gluconeogenesis

N.B Careful control of DM by insulin is based on measuring of HbA_{1c}

Hypoglycemia

- Insulin is not required for glucose utilization by brain.

• Causes of hypoglycemia:

- 1 Overdose of insulin in DM
- 2 Insulinoma (tumour of pancreas)
- 3 Large malignant tumours outside pancreas secrete excess IGF_{II}

• Manifestations:

- 1 — bl. glucose $< 70\text{mg}$ autonomic changes e.g palpitation, sweating & nervousness.
- 2 At lower glucose level $< 50\text{mg}$ neuroglycopenic symptoms as hunger, confusion and other cognitive abnormalities.
- 3 At even lower glucose level $\rightarrow$ lethargy, coma, convulsions & eventually death.

End
(56)

Good Luck 09

hypothalamo : hypophyseal

TRACT

- ADH
- Oxytocin

Pack of hypothalamus

Neurons connection

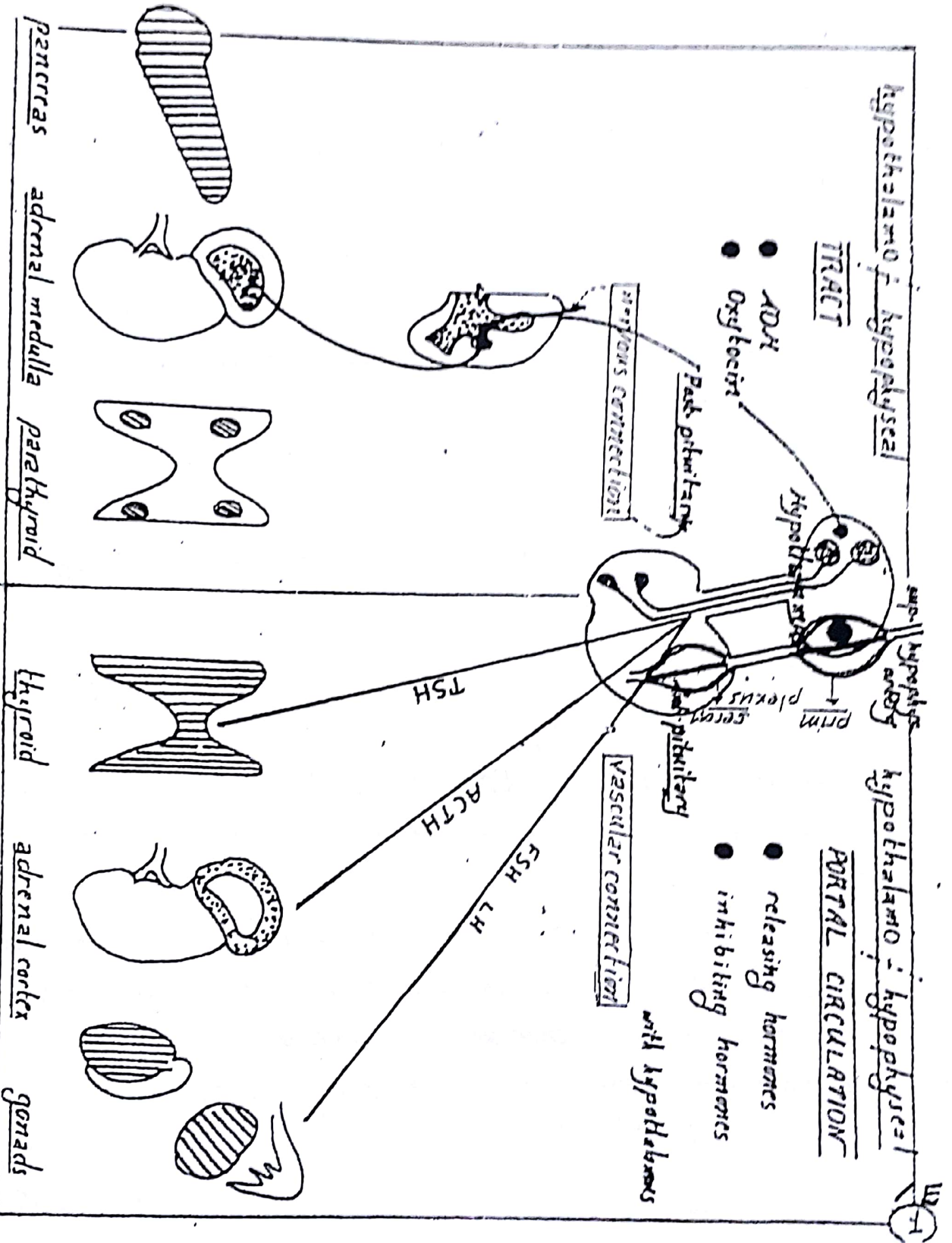
hypothalamo : hypophyseal

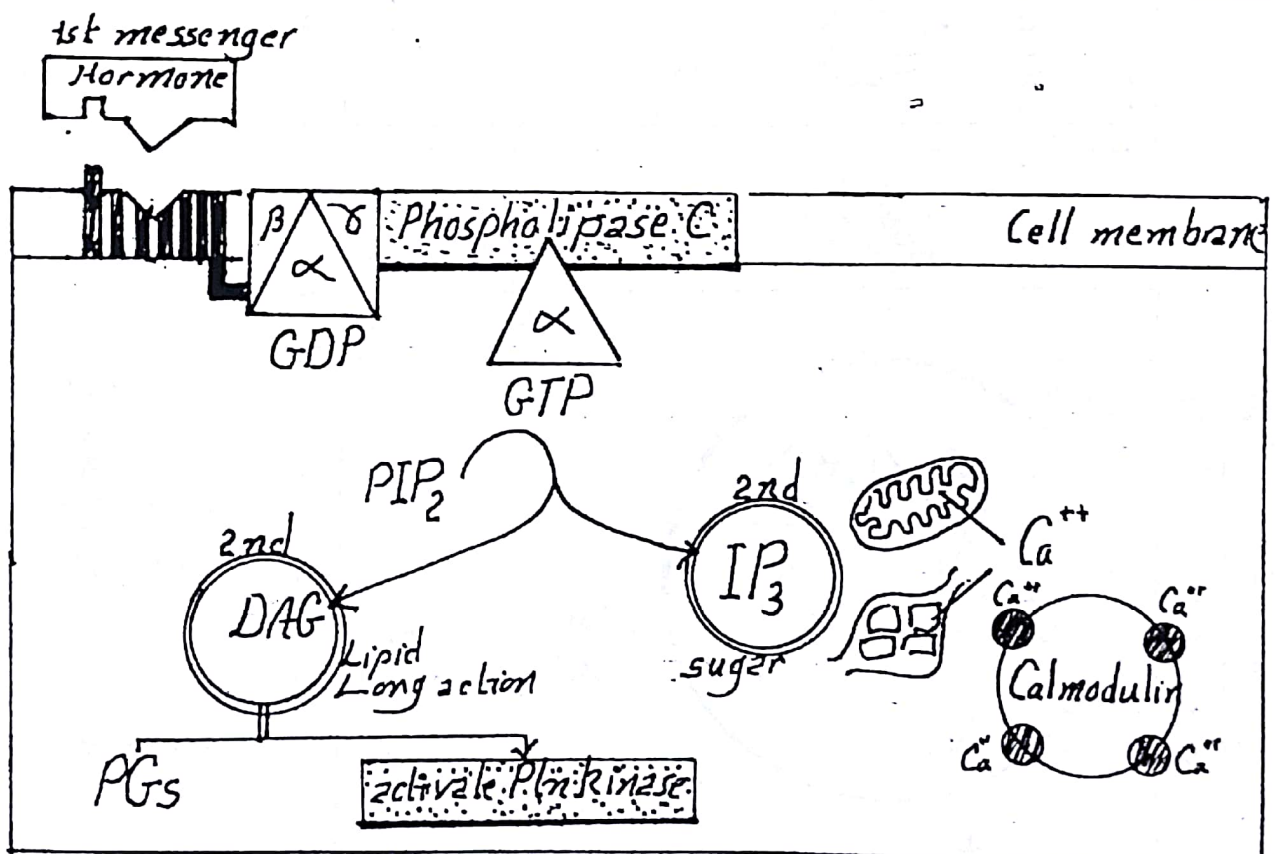
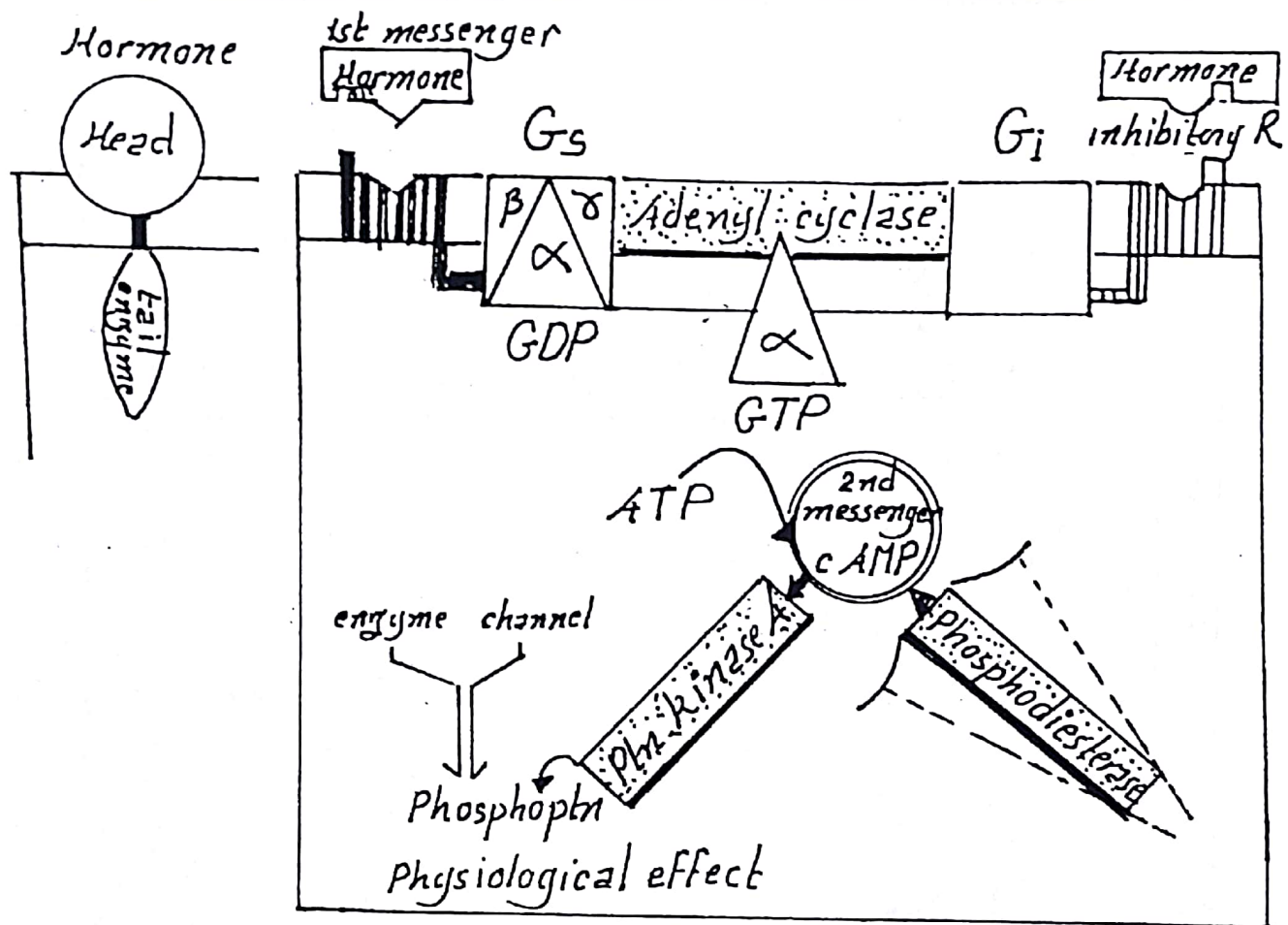
PORTAL CIRCULATION

- releasing hormones
- inhibiting hormones

with hypothalamus

Vascular connection





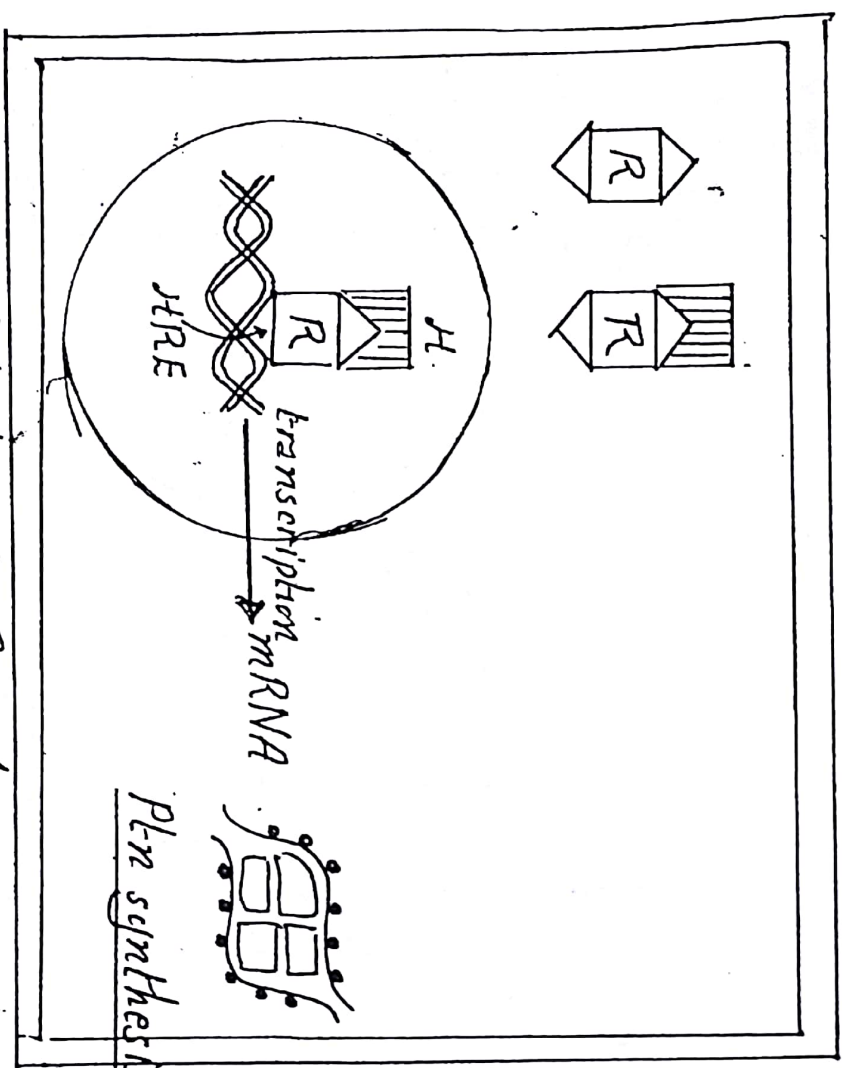
Mechanism of action of:

Steroid Hormone

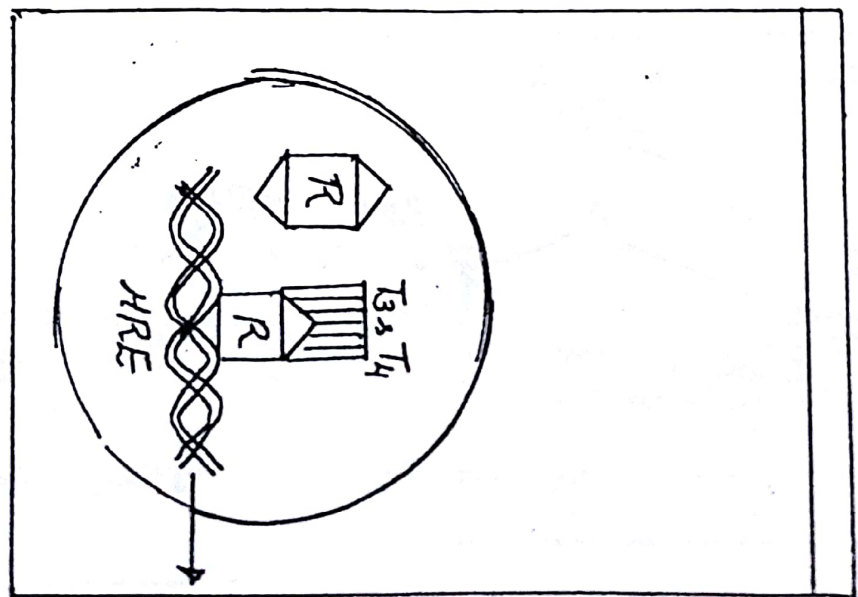


Sex hormones
Adrenal cortical hormones
Vit D₃

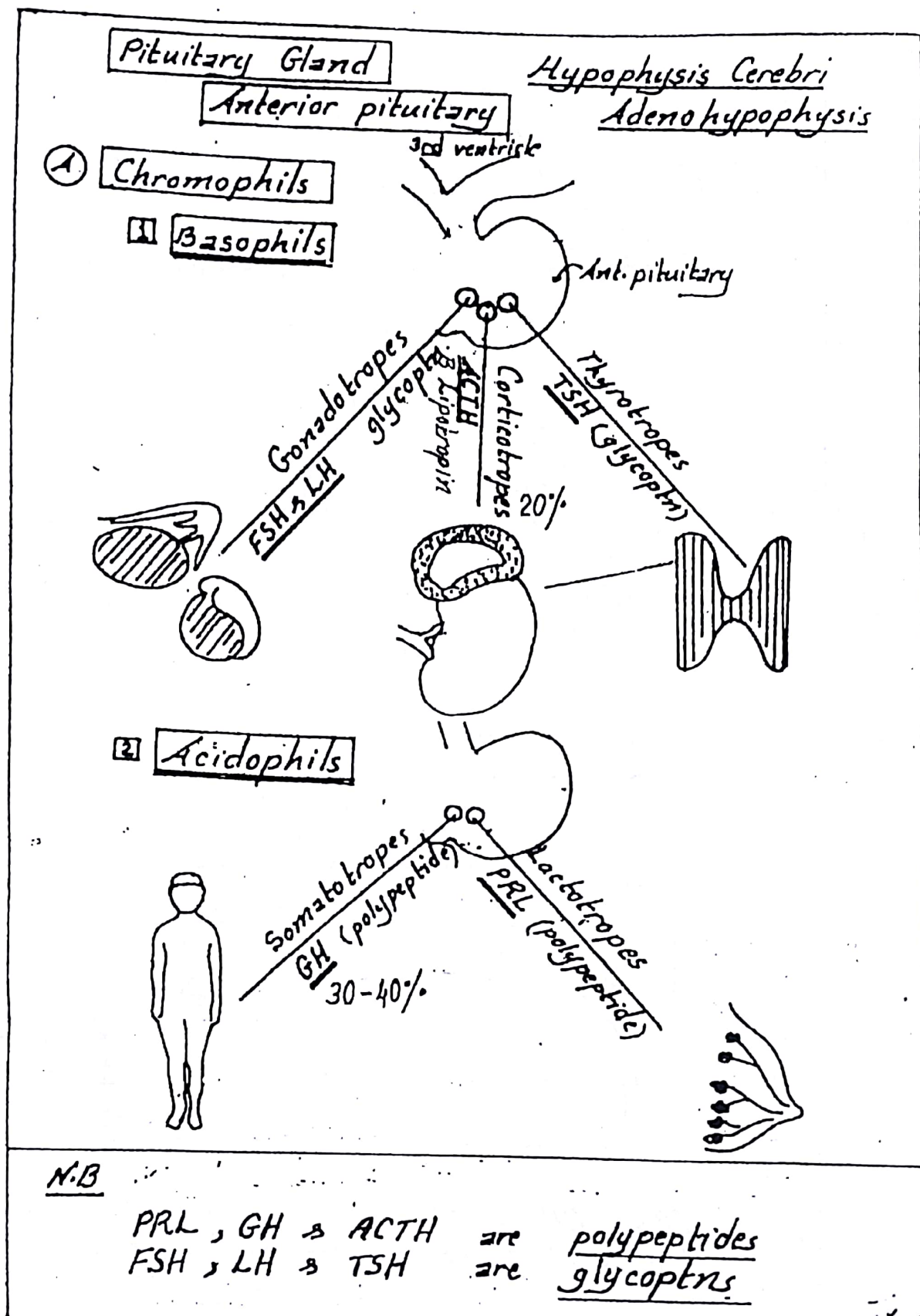
T₃ and T₄

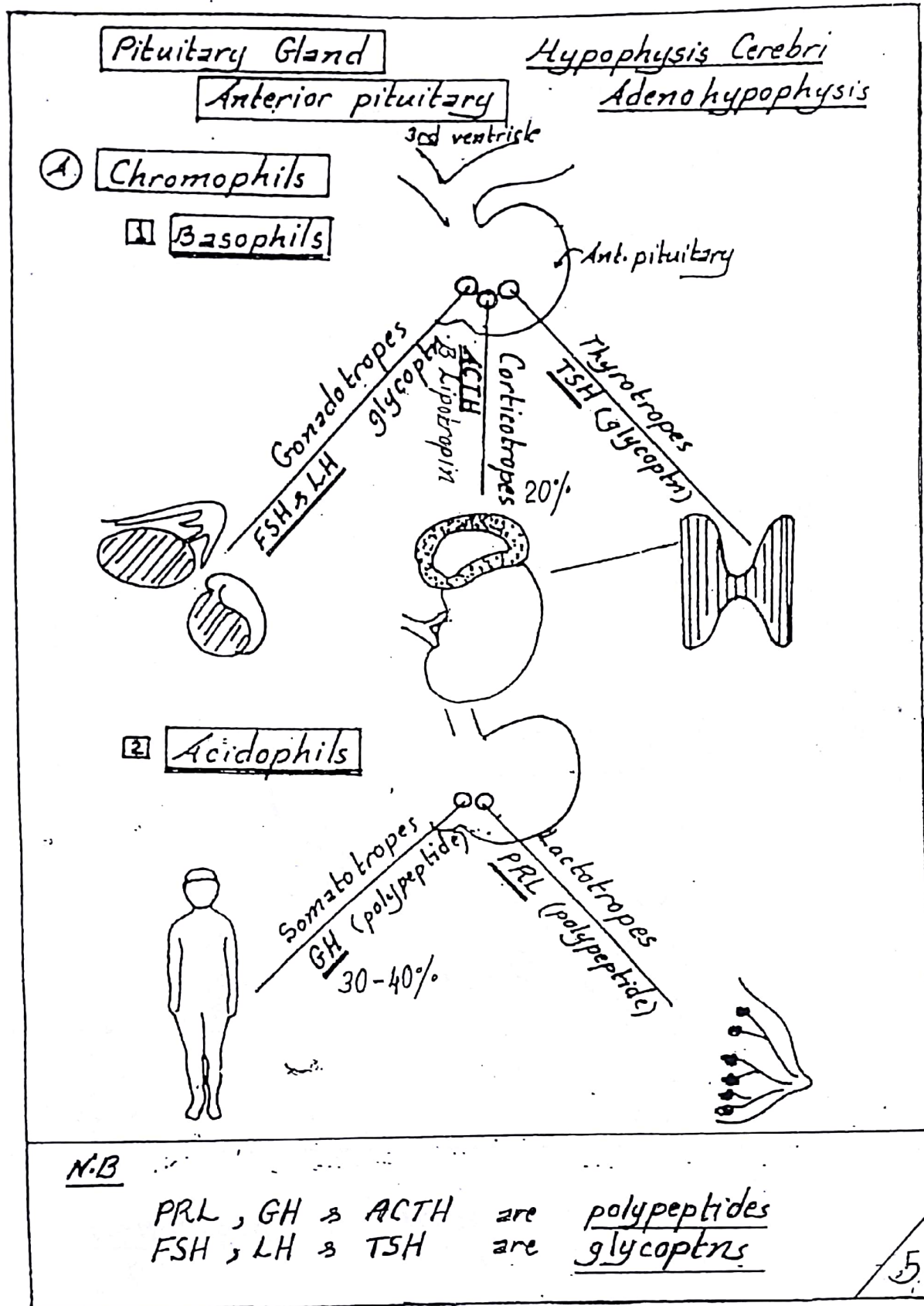


- Cytoplasmic Receptors

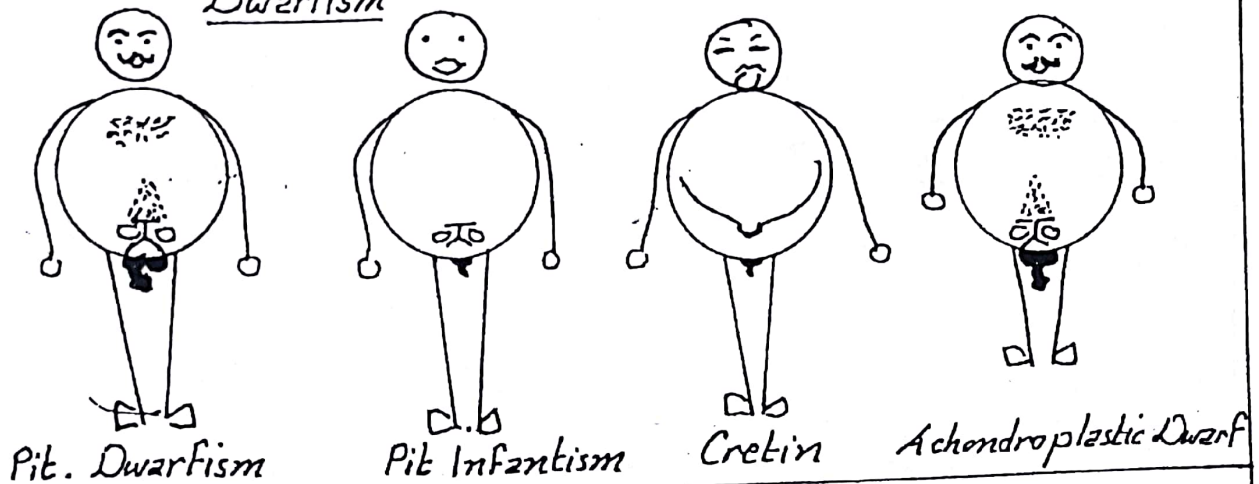


- Nuclear receptor
- More enzyme
- Longer action





Dwarfism



Acromegaly

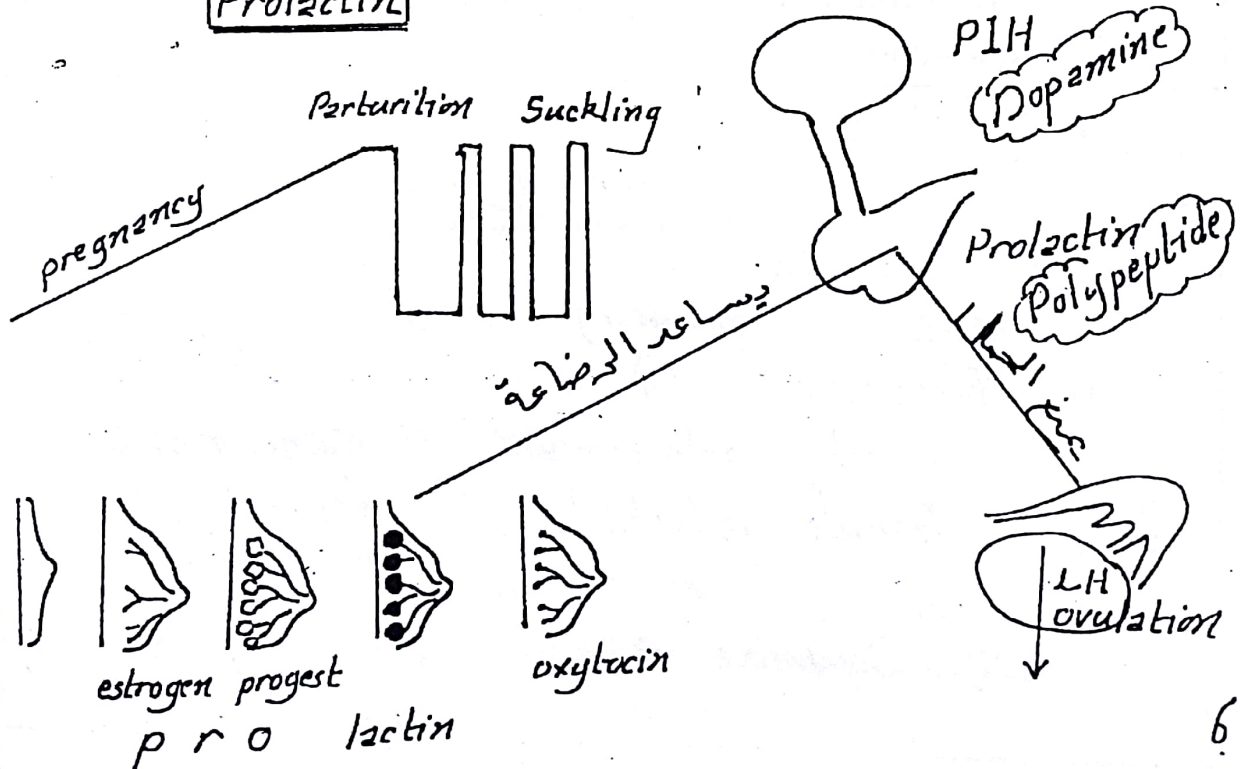
Bones Skull
Hands & Feet
Vertebrae

Soft t Forehead
Pituitary
Thyroid
Breast
Viscera
Muscles

Hypoglycemia & DM
Acromegalic giant

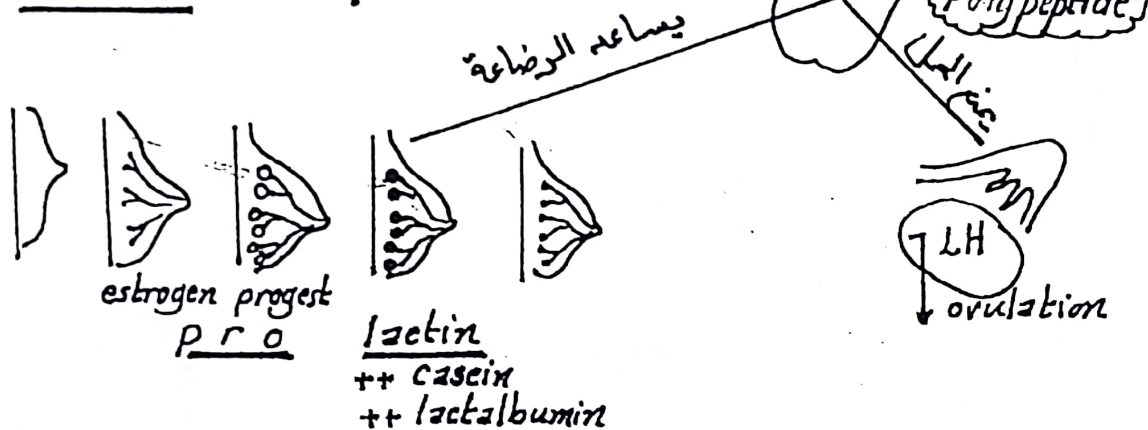


Prolactin

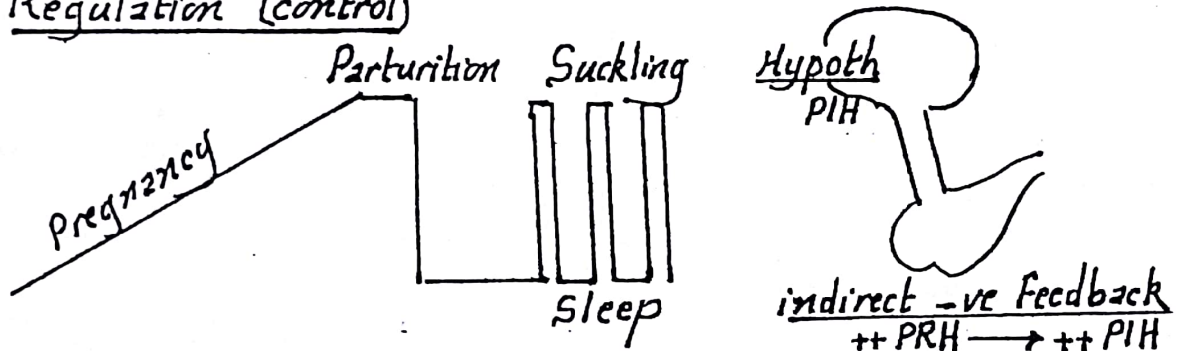


Prolactin

Chemical nature : polypeptide
Site of release : lactotropes
Mech. of action : JAK STAT
Actions :



Regulation (control)



Disorders :

Hypo rare

Hyperprolactinemia

Cause

pituitary tumour.

Effect

♀

♂

breast

galactorrhoea

gynecomastia

Gonads

infertility

infertility

amenorrhoea

tt Dopamine AGONIST e.g bromocriptine

(7)

ADH **Vasopressin** **Pressophysin**

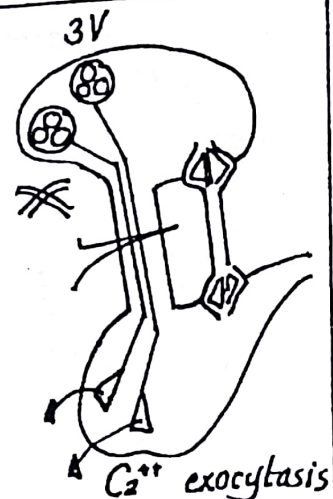
Chemistry : Nonapeptide

Formed : Supraoptic nucleus as prepro

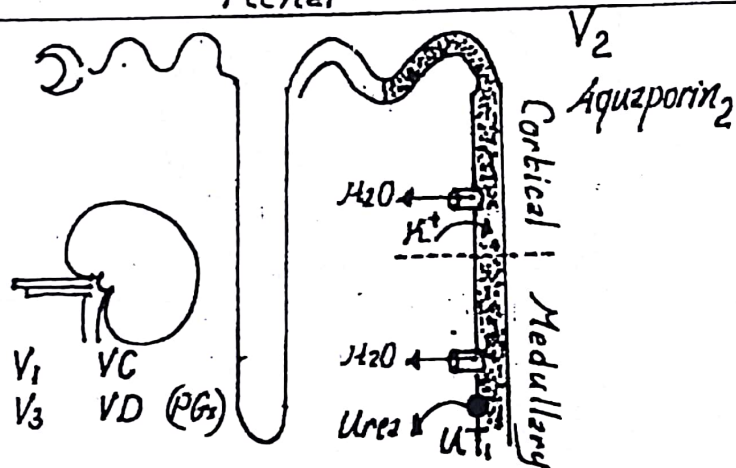
Migrate : Hypoth. Hypoph. tr as pro

Release : A. pot. Ca^{++} dependent exocytosis

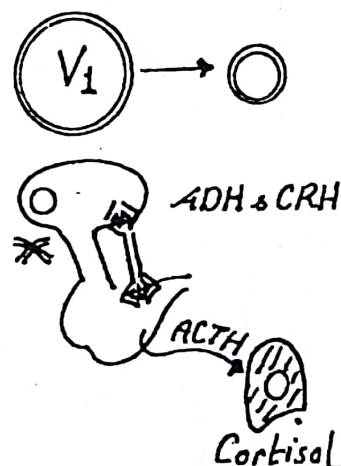
Receptors : V_1 — IP_3 Ca on bl. vs
 V_2 — cAMP on nephron
 V_3 — PGs on renal vessels



Action : Renal



Extrarenal



Control : Increased ADH

- 1 ++ plasma OP 10%
- 2 -- blood volume 10%
- 3 Beta adrenergic agonists
- 4 Drugs Morphine & nicotine
- 5 Stress

Decreased ADH

- 1 -- plasma OP
- 2 ++ blood volume
- 3 Alpha adrenergic stimulants
- 4 Drugs beer (Alcoholics)

Disorders :

Diabetes insipidus DI

Causes 1 Central DI
 2 Nephrogenic DI

V_2
 AQP2

Effects 1 Polyuria low sp. gr
 2 Polydipsia if n't death

Water intoxication

- 1 CNS diseases
- 2 tumour lung panc.

- 1 -- OP
- 2 swelling of brain cells

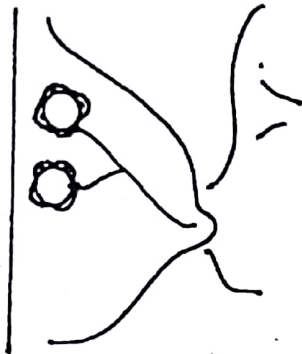
Oxytocin

Formed

Actions

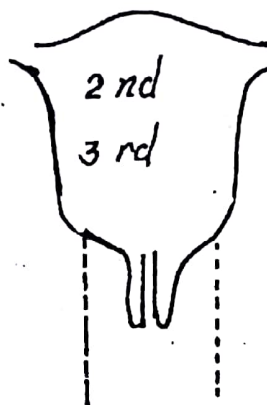
Suckling

contraction



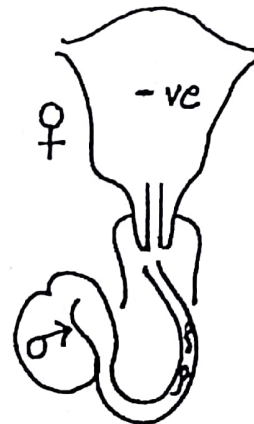
Labour

contraction



Sexual intercourse

contraction



Mech of action

via G ptn $\rightarrow$ $IP_3 \rightarrow ++Ca^{++}$

Control

Neuro hormonal Reflex

1 Stimulus

1 Massage of nipple

Suckling

Sexual play

Unconditioned

receptors of nipple

Conditioned

no receptor stim of nipple.

2 Dilatation of cervix

3 Genital stimulation

2 Afferent

Impulses via sp cd

3 Centre

Hypothalamic nuclei

4 Efferent

Hormone (oxytocin)

Thyroid gland

— Highly vascular

5 ml / g / min

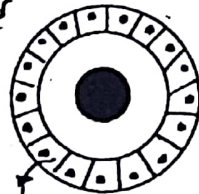
— Hormones

Iodinated Hormones

T_4 thyroxine

T_3

A cells of follicles



Calcitonin CT

C cells

Parafollicular cells

— Iodine

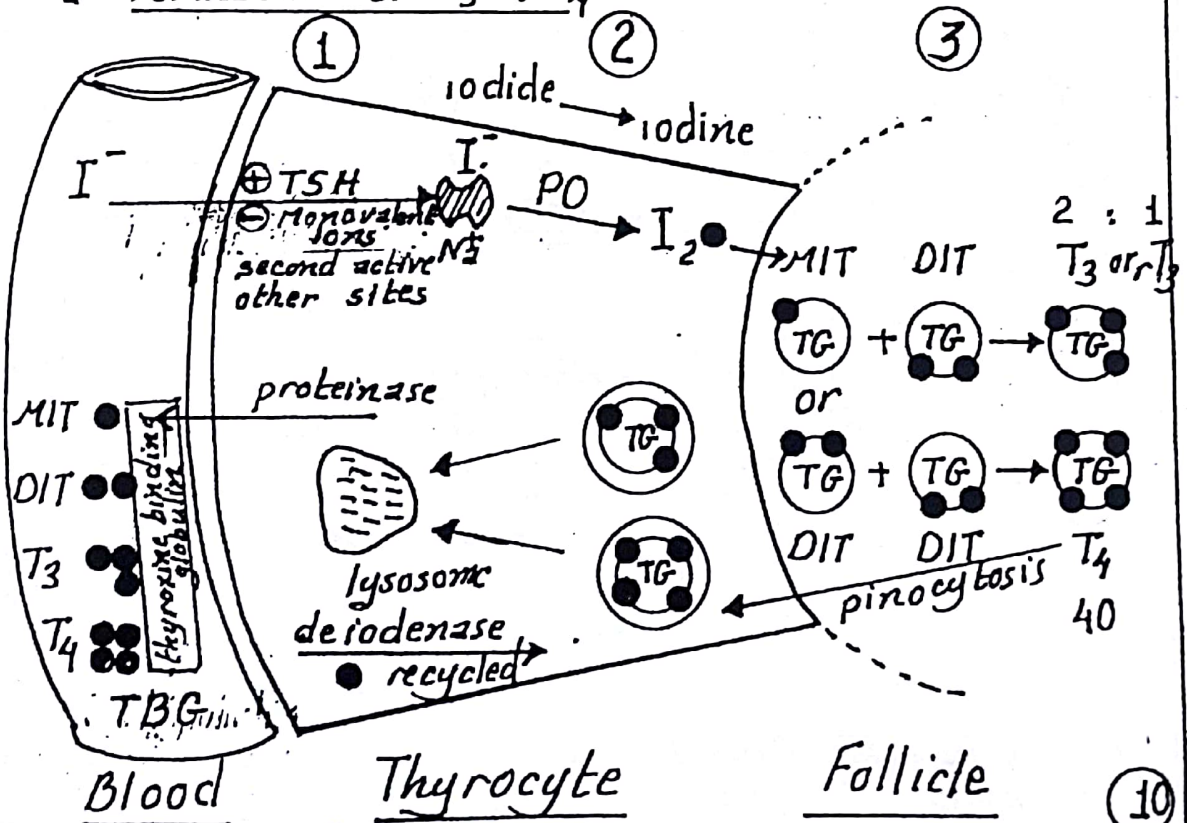
500 / day μg $\left[\begin{array}{l} \frac{1}{5} \rightarrow T_3, T_4 \rightarrow I_2 \rightarrow \text{urine} \\ \frac{4}{5} \rightarrow \text{urine} \end{array} \right.$

— Follicular cavity large reserve of T_3, T_4 Thyrocytes small reserve of T_3, T_4

— Functions of Follicular cells

1 Thyroglobulin synthesis (TG) rich in tyrosine (123).

2 Formation of T_3 & T_4



● Plasma ptn binding

- Globulins α_1, α_2 (TBG) higher affinity $\frac{2}{3} T_4$ & $\frac{1}{2} T_3$
- Albumin & prealbumin " capacity

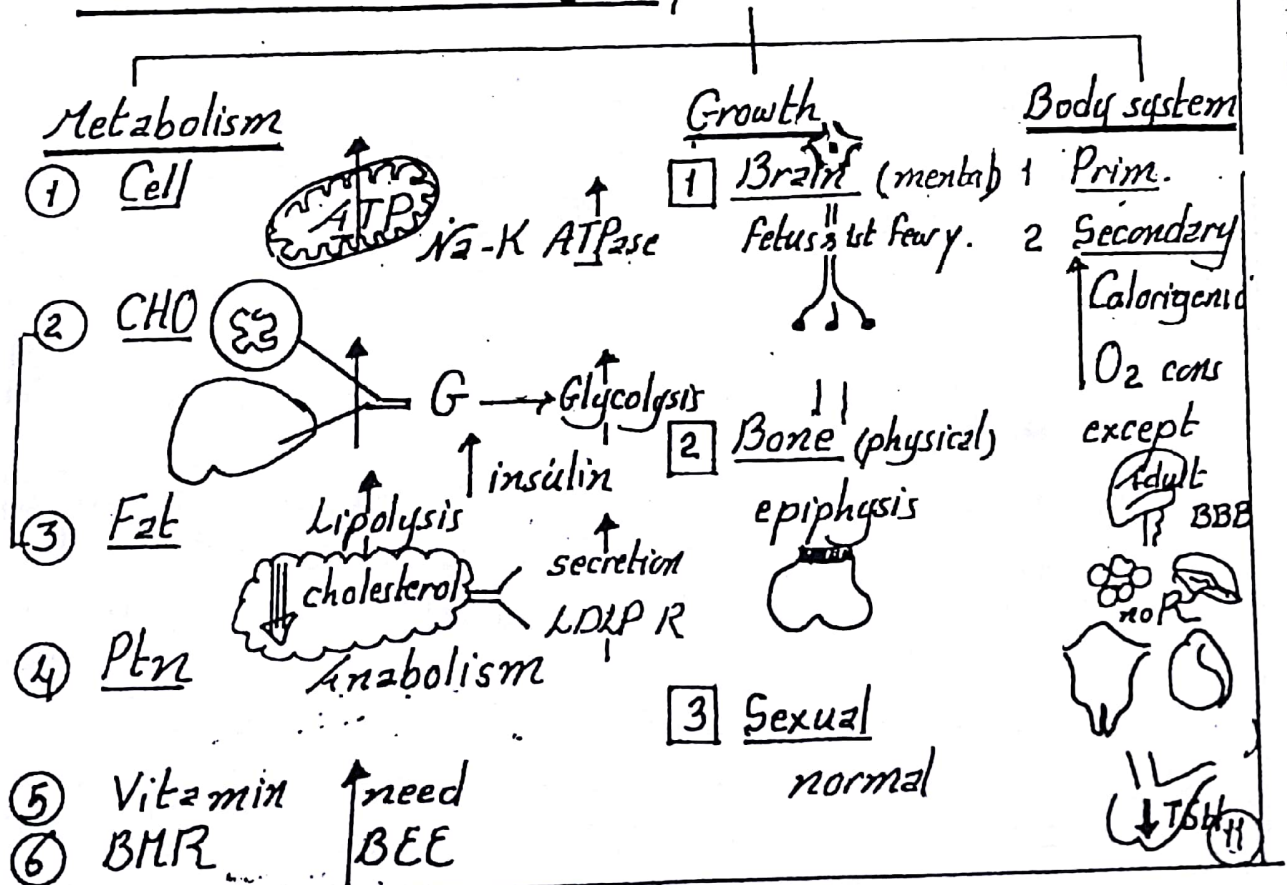
● Rate of secretion

Total
Bound
Free

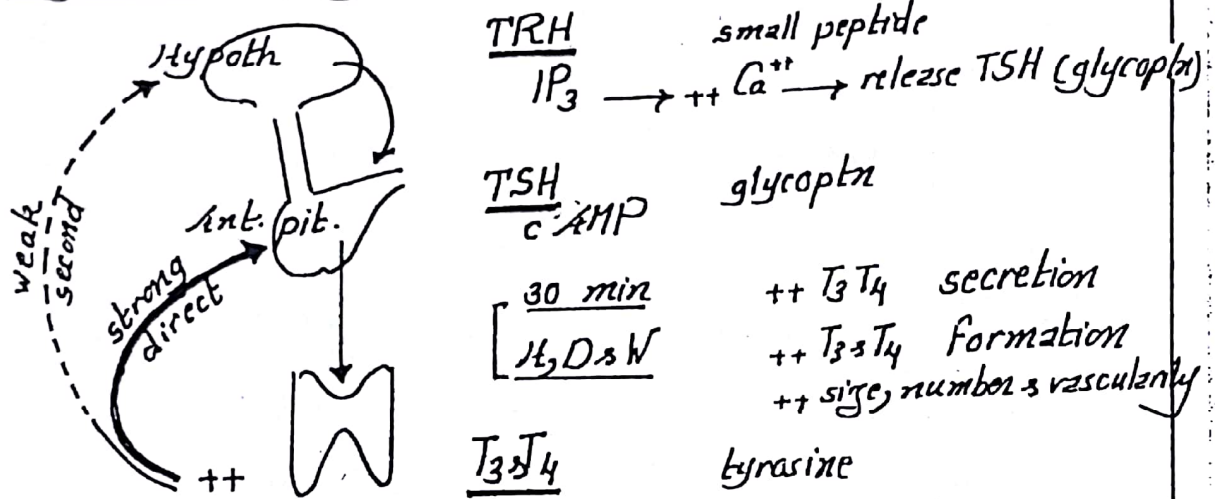
T_4 93%	T_3 7%
8-12	0.15 $\mu g/dl$
99.98	99.80
2	0.3 ng/dl
	More free More affinity to receptors

- Tyroid receptors (TR) 4 types α_1, α_2 β_1 & β_2
- T_4 binds to 4 T_3 binds to 3 except α_2
- Nuclear R i.e genomic Extranuclear nongenomic
- TR has ligand binding & DNA binding domain

● Functions effects of T_3 & T_4 3



● Regulation of thyroid gland

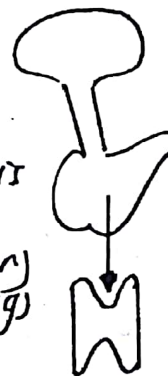


● Disorders Hypo or Hyper Prim. or Second.

- Hypothyroidism

Causes: thyroidal

- C [Congenital
 Chronic thyroiditis
 Chronic -- I_2
 D [Maternal (mother)
 Iatrogenic (drug)



suprathyroidal

Pituitary: secondary

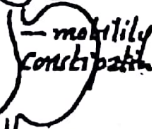
Hypoth: tertiary

Effects:

General

1 ↓ Calorigenesis

- a PE susceptible to cold
 b ++ body weight
 nonpitting edema
 c -- activity of body system



2 Skin coarse, dry & yellow

Carotene $\xrightarrow{\text{T}_3 \text{ \& } \text{T}_4}$ Vit A

3 Laboratory

a ↑ cholesterol

b ↓ $\text{T}_3 \text{ \& } \text{T}_4$ HIGH TSH thyroidal
 ↓ $\text{T}_3 \text{ \& } \text{T}_4$ LOW TSH suprathy

Specific (Age related)

1 Cretinism

infant

1 Dwarf: Bones soft

2 Idiot:

3 Impotent & sterile

4 Special characters 5



2 Myxedema

1 Mental Apathy & -- RT

2 Sexual Atrophy of gonads

3 Husky voice
absent outer 1/3 of eye brows (12)

Hyperthyroidism

Causes:

Thyroidal

Grave's disease

Autoimmune disease (Ab)
TSH R [stim] Ab

Acute thyroiditis or Tumour

Supra

Pit. tumour or resistance of pit. receptors

Extra

Ectopic thyroid t or excess intake of T_4

Effects:

1 ++ BEE + 100%

← Pt can't tolerate hot.
-- body weight
skin warm sweaty red

↑ PP = $\frac{S}{SV} - \frac{D}{VD}$

2 Body system (++ BEE & ++ sensitivity to catecholamines)

+

HR
PP

3 Exophthalmos 50% | Cause auto Ab
Effects Dryness of eyes

tremors
hyperreflexia

4 Goitre

5 Laboratory

a ↓ cholesterol

b ↑ T_3 T_4 LOW TSH thyroidal & extra
↑ T_3 T_4 HIGH TSH supra thyroidal



• Antithyroid drugs: Goitrogenic drugs

1 Interfere with iodide trapping
competitive inhibition

Monovalent anions

e.g. Thiocyanates

2 Block organic binding

e.g. Thiocarbamide

Drugs 1 & 2 -- T_3 & T_4 -ve feedback → ++ TSH → Goitre

3 Medical thyroidectomy Radioactive iodine.

• Goitre:

Enlargement of thyroid with ++ or -- or normal T_3 & T_4 .

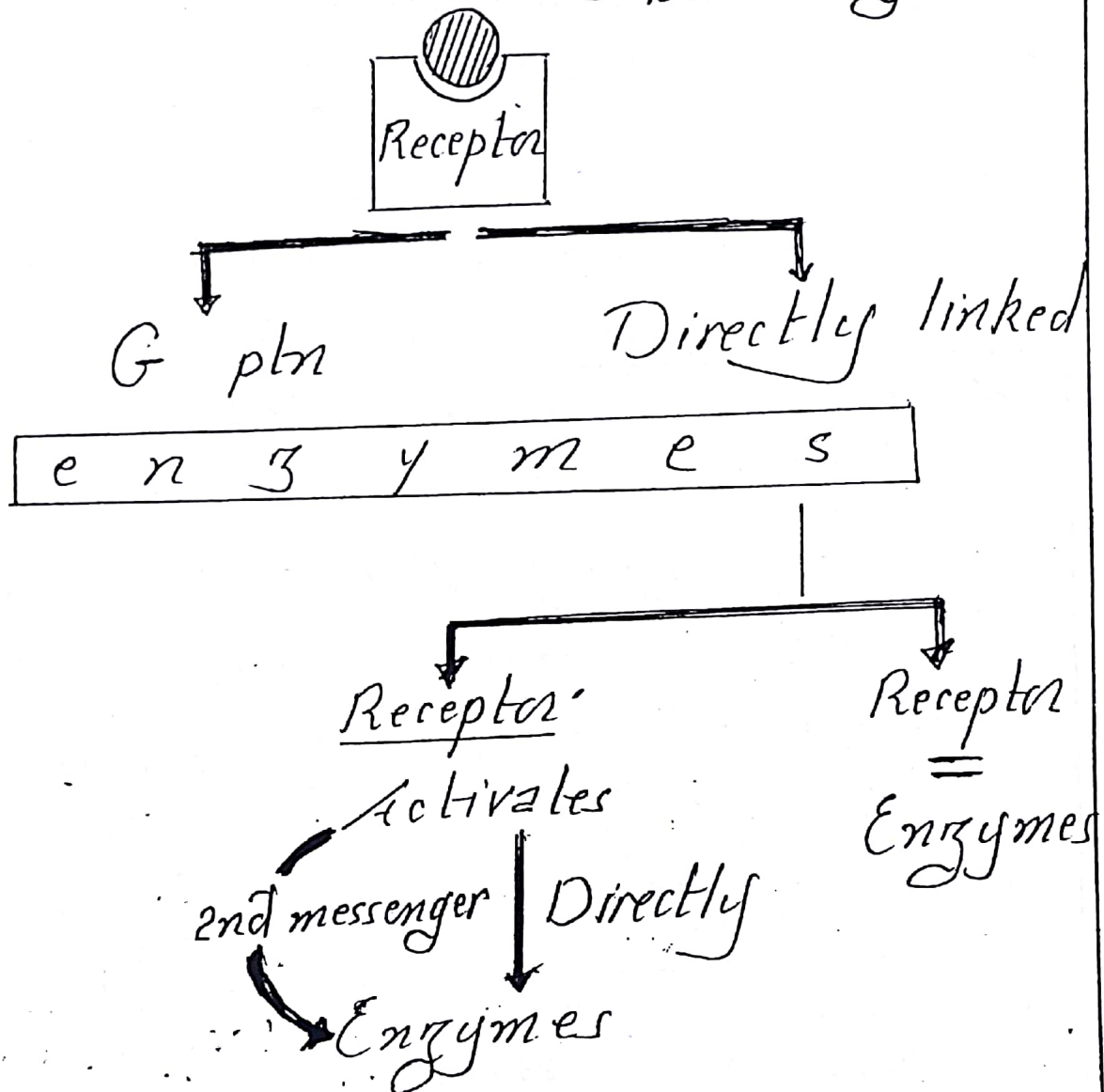
a Physiological : ♀ during puberty, pregnancy or lactation

b Hypothyroidism : Severe -- I_2 or TSH-R [block] Ab

c Hyperthyroidism : Grave's disease TSH-R [stim] Ab (13)

d Nodular goitre : Hot (active) or cold (inactive) nodules

Nongenomic insoluble in lipid
Hormone 1st messenger



2nd messenger

- 1 cAMP → Mostly
- 2 IP_3 & DAG → Ca^{++} { Contract
Exocytosis
- 3 Ca^{++} Calmodulin
- 4 cGMP

Functions of Calcium :

A) Ionised calcium 1, 2, 3 < 1%

- | | | | |
|----------------|--------------------------|---------|-------------------------------|
| 1 Bl. clotting | 2 2nd messenger | Hormone | 4 nerve & muscle excitability |
| 3 secretion | 5 muscle contraction | | |
| | 6 Cardiac ms rhythmicity | | |

B) Calcium salts

> 99%

Hard tissues : Bone & teeth

Soft tissues : Milk

Distribution of calcium :

A) Plasma 9-11 mg % < 1/2 g

- | | | | |
|----------------|-----|----------------|----------|
| 1 ionised | 50% | Diffusible | Active |
| 2 complexes | | Diffusible | Inactive |
| 3 bound to pln | 45% | Non diffusible | Inactive |
| mainly albumin | | | |

B) Bones 1100 g > 99%

Absorption of Ca^{++} : 30-80% Upper small intestine

- ++ solubility
- ++ absorption
- | | |
|---------------------------------|--|
| 1 Acidity | |
| 2 Amino acids i.e pln meal | |
| 3 Acidic Food e.g yogurt | |
| 4 Active Vitamin D ₃ | |

Note:

- Ca citrate soluble
- Ca oxalate insoluble
- Ca phosphate "

Phosphorous : 500 - 800 g

- Bone & teeth 85 - 90 %

- Plasma level 12 mg /dl

$Ca^{++} \times PO_4^{--} = \text{solubility product}$ depends on pH

ECF is supersaturated with Ca^{++} & PO_4^{--}

Pyrophosphate compound inhibits $\leftarrow$ Ca precipitation PO_4

Precipitation occurs :

- 1 Physiologically osteoblasts secrete pyrophosphate inhibitor
- 2 Pathologically in atherosclerosis & degenerated cells

Ca homeostasis :

1 First line

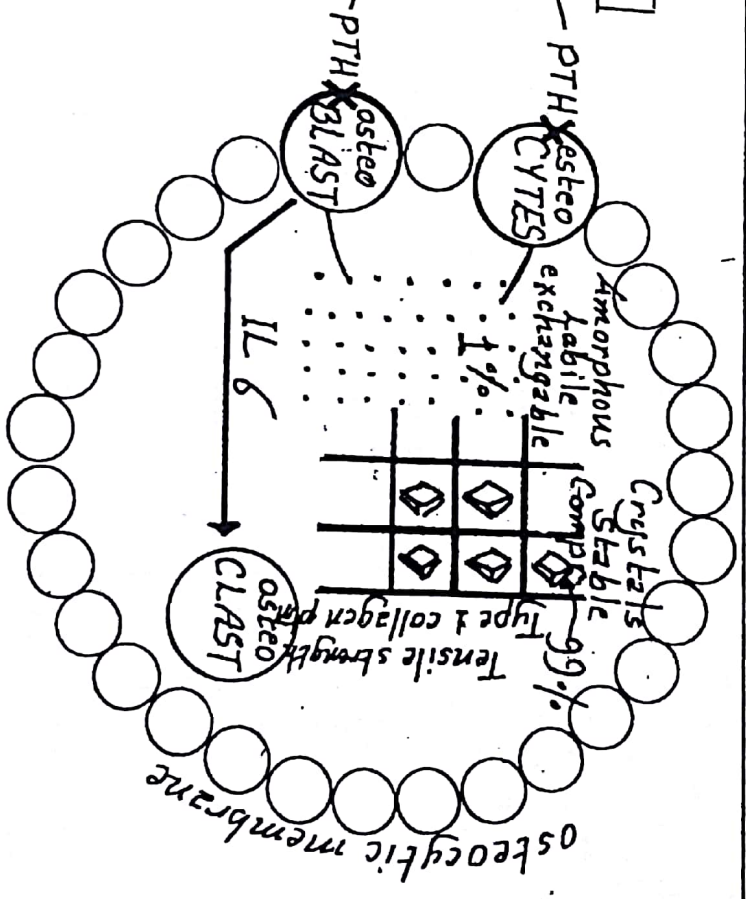
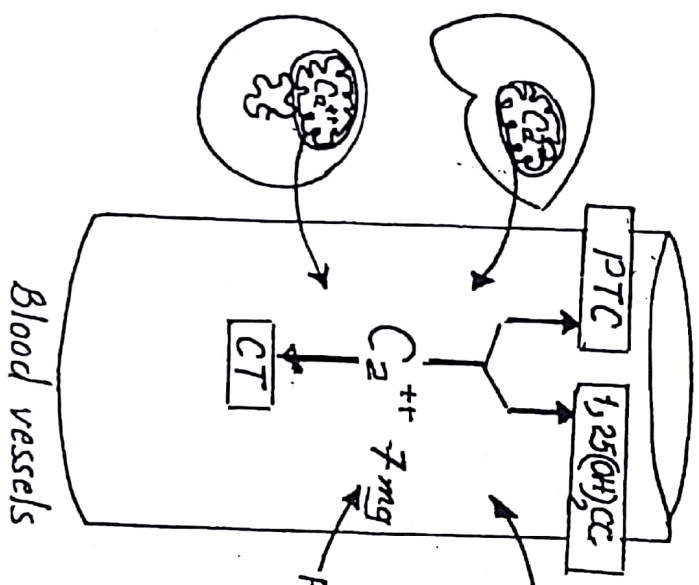
- Exchangeable Ca^{++}
- Mitochondria

2 Second line

- Ca raising hormones:

PTH & $1,25(OH)_2CC$

- Ca lowering hormone: CT



Bone remodelling
4% of compact bone
20% of trabecular
per year

Osteoblast

Bone building cells

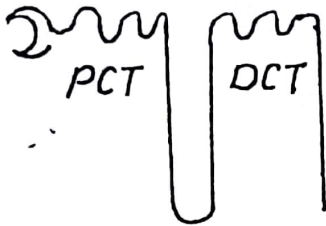
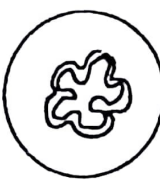
- 1 Collagen & other pths
- 2 Alkaline phosphatase
- 3 Pyrophosphate inhibitor

Osteoclasts

Bone eating cells

- 1 H^+ ions dissolve crystals
- 2 Acid protease dissolves collagen

Osteocytes : exchange of Ca^{++}

	Bones	Kidney	Intestine
<u>PTH</u> polypeptide 84 aa	 resorption rapid min. to hours $++$ Ca^{++} pump. slow days to weeks stim. osteoclast.	 reabsorption $\downarrow PO_4^{=}$ $\uparrow Ca^{++}$ $++$ $1,25(OH)_2 CC$ via 1α hydroxylase. $++$ Mg^{++} & H^+ reabsorp.	 absorption $\uparrow Ca^{++}$ viz $1,25(OH)_2 CC$ viz Calbindin D
<u>CT</u> polypeptide 32 aa	bone building -- osteo <u>CLAST</u> [number activity] $++$ osteo <u>BLAST</u> [activity]	$\downarrow PO_4^{=}$ $\downarrow Ca^{++}$ -- 1α hydroxylase.	—
<u>$1,25(OH)_2 CC$</u>	resorption if Ca^{++} & $PO_4^{=}$ are high. bone building if Ca^{++} & $PO_4^{=}$ are low.	$\uparrow PO_4^{=}$ $\uparrow Ca^{++}$ $++$ calbindin D	absorption $\uparrow Ca^{++}$ viz Calbindin D
<u>Regulation</u>	PTH $\uparrow$ PTH -- plasma Ca^{++} $++$ " $PO_4^{=}$ $++$ cAMP i.e. β adrenergic stim. $\downarrow$ PTH $++$ plasma Ca^{++} $++$ $1,25(OH)_2 CC$ PTH receptors: 1 <u>PTH/PTH rP</u> on osteo Blasts & osteocyte 2 <u>PTH 2R</u> on placenta, pancreas, brain 1 & 2 via G-s $\rightarrow ++$ cAMP G-q $\rightarrow ++$ intracellular Ca^{++} 3 <u>cPTH</u> binds to C terminal of PTH	CT $\uparrow$ CT $++$ plasma Ca^{++} β adrenergic stim GIT hormones gastrin, CCK Estrogen, prolactin & dopamine $\downarrow$ CT -- plasma Ca^{++}	$1,25(OH)_2 CC$ $\uparrow$ $1,25(OH)_2 CC$ -- plasma Ca^{++} viz $++$ PTH. $\downarrow$ $1,25(OH)_2 CC$ $++$ $1,25(OH)_2 CC$ viz -ve feed back by -- 1α hydroxylase
		Formation of $1,25(OH)_2 CC$: 7 dehydrocholesterol $\xrightarrow[\text{infrared}]{\text{ultraviolet}}$ cholecalciferol CC (Vit D₃) CC $\xrightarrow{OH}$ $25(OH) CC$ $25(OH) CC \xrightarrow[\text{activates } 1\alpha \text{ hydroxylase}]{\text{PTH in PCT}}$ $1,25(OH)_2 CC$ (3)	

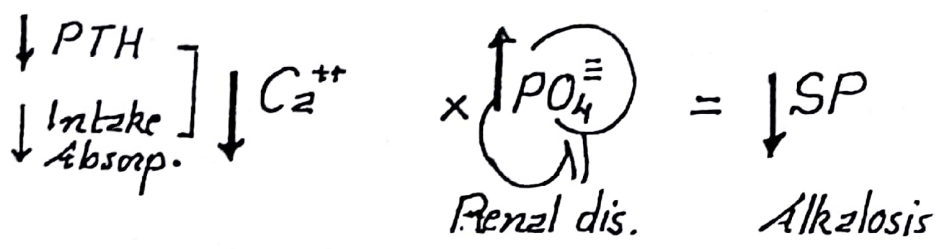
Tetany

• Definition :



--- Ca^{++} --- threshold voltage gated Na channels

• Causes :



• Types :

Manifest :

Latent : (Hidden)

← 7mg —————→ 9.4 mg/dl

• Manifestation during rest.

• No manifest. during rest.

• Fibrillary twitches
• then clonic
• then tetanic :

Diagnosis :

1 -- plasma Ca^{++}

2 Provocation tests :

• carpopedal spasm.
• laryngeal resp. "



Chvostek



Trousseau
accoucheur



Erb signs

Treatment :

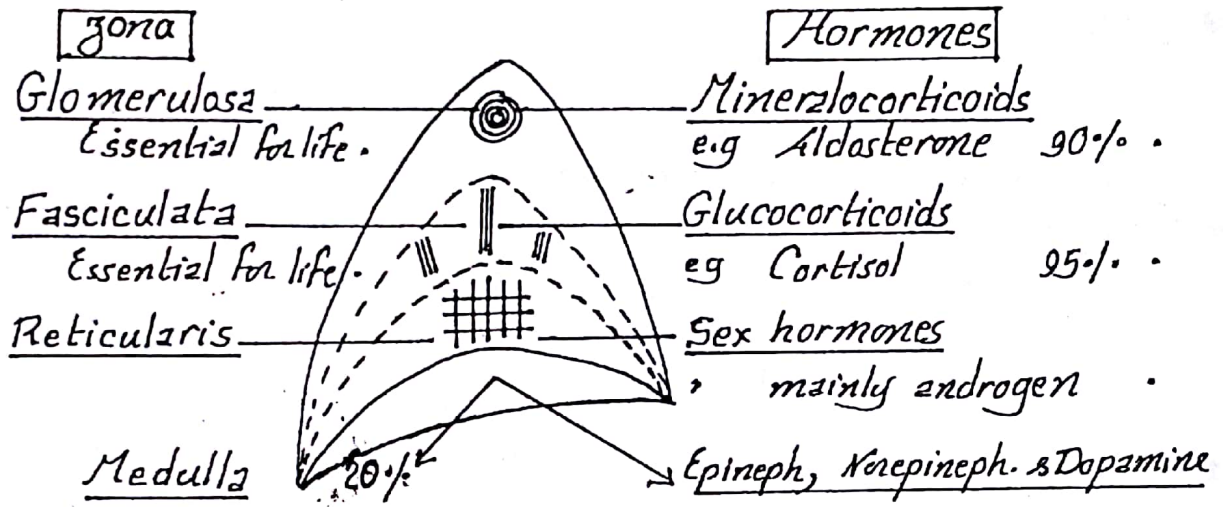
1 Ca gluconate 10 ml 10% .
slowly
to avoid Ca rigor of heart

1 Diet rich in calcium.
2 Vitamin D (absorp.)
3 Acidifying salt (ionisat.)

Treatment of cause
alkalosis or renal failure.

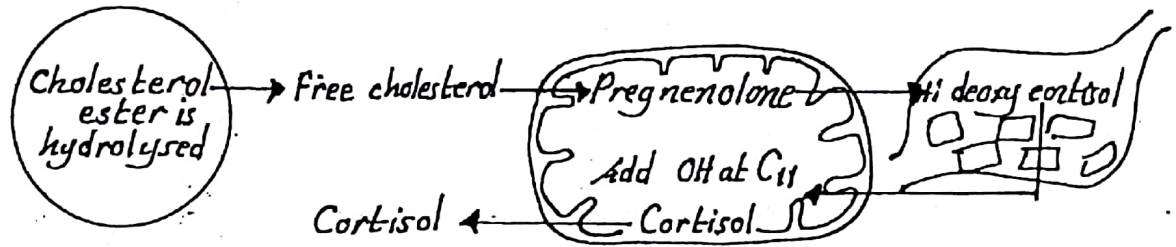
Adrenal gland

Essential for life.



Synthesis of adrenocortical hormones : Steroids
Cholesterol < From plasma by endocytosis -
 Small amount formed in cortical cells.

Glucocorticoids 95% Cortisol 4% corticosterone
 • Formation : mainly in Z. fasciculata also in Z. reticularis



Vacuole Mitochondria E. reticulum.

• Transport in blood : 75% Globulin CBG = transcortin.
 15% Albumin
 10% Free

CBG -- in hepatic cirrhosis & nephrosis ++ by estrogen (pregnancy)

• Metabolism and excretion :

Most cortisol is reduced & conjugated to glucuronic acid & excreted in urine.
 Liver diseases, surgery & stresses → ++ free cortisol (5)

Actions of Glucocorticoids : 3

- Permissive actions : Low level . is needed .

- 1 Glycogenolysis by glucagon .
- 2 Lipolysis by catecholamines and GH .
- 3 VC of arterioles by " and angiotensin II .

- Physiological actions : Normal level .

① Metabolism :

A CHO

Diabetogenic .

- 1 Gluconeogenesis ++ extrahepatic ptn catabolism → ++ aa.
++ hepatic uptake of aa.
- 2 -- glucose utilization by muscle and adipose tissue.
↓ affinity of insulin R ↓ mobility of G. transporter ↓ phosphoryl.

B Ptn

Extrahepatic catabolism .

-- aa transport into ms & adipose t ++ aa transport into liver cells

C FAT

Lipolysis .

++ activity of lipase ... if -- insulin e.g DM → ketogenesis .

② In stress : Antistress .

++ glucose & FFA (energy) , ++ aa (repair) & pressor (permissive)

③ On appetite : 2 opposing effects :

++ appetite (++ neuropeptide Y & CRH) -- appetite (++ leptin)

④ CVS :

Maintenance of normal ABP

inotropic ++ β recept. ++ Na^+ -K ATPase , -- VD (by -- PGs) & maintains of bl. volume (-- vascular permeability) .

⑤ Blood cells :

++ RBCs , platelets & neutrophils but -- function of neutrophils .
-- eosinophils -- T lymphocytes .

⑥ CNS :

modulates excitability , behaviour and mood of individuals .
-- REM sleep ++ slow wave sleep ++ awake time

⑦ Sk m :

++ A choline → ++ NM transmission & contraction (6)

⑧ Kidney : H_2O load rapid excretion ++ GFR Acid load ++ NH_4^+ excretion ++ PO_4 excretion

⑨ Other effects : slight mineralocorticoids Maturation of surfactant

● Pharmacological actions

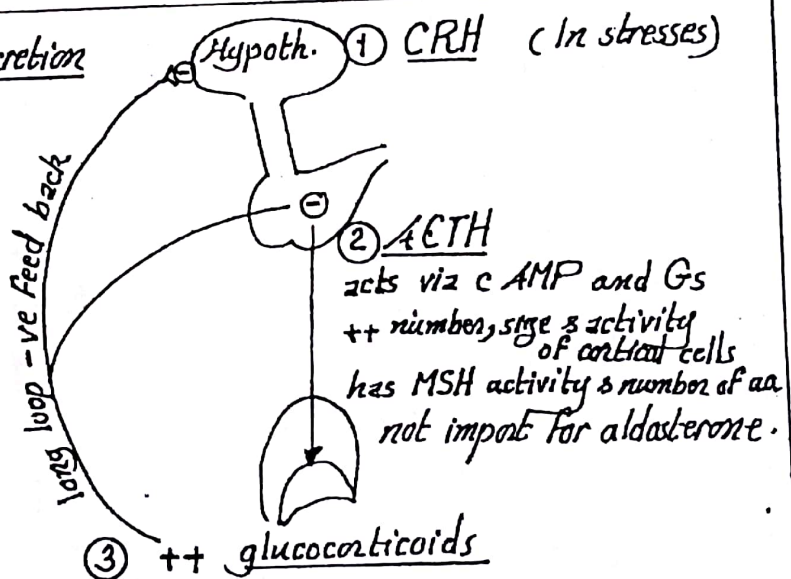
High level .

- 1 On Bones : Osteoporosis
 -- bone formation -- osteoblasts -- type I collagen Anti vit D
 ++ bone resorption
- 2 On connective tissue : -- collagen synthesis & -- Fibroblasts
- 3 Anti inflammatory : Stabilises lysosomes & -- IL-1
- 4 Anti allergic : -- histamine release -- leukotriens format
- 5 Immunity and lymphoid tissues : -- humoral & cellular immunity
 -- Ig , -- T cells & -- interferon.

● Control of glucocorticoid secretion

④ Circadian rhythm
 Neuronal
 Related to cycles of stress
 ++ in early morning

⑤ Large dose of
vasopressin, serotonin
& VIP stimulate
cortisol secretion



Mineralocorticoids

Transport

Metabolism

Aldosterone 90% Desoxycorticosterone $\frac{1}{60}$ effect
 60% is bound to transcortin and albumin.
 Binding is weaker than for cortisol i.e. shorter $\frac{1}{2}$ life.
 90% is cleared by liver in a single passage
 reduced & conjugated then excreted in urine.

End

④

- Action of aldosterone : maintains ECF vol. by conserving Na^+ .

[1] On kidney: Distal & collecting T. :

[a] P cells : ++ $\text{Na}^+ - \text{K}^+$ exchange

Aldosterone-receptor complex

++ ptn synthesis via mRNA

(1) ++ reabsorption of Na^+

Luminal border basolateral border

Passive

Active

Ptn channels

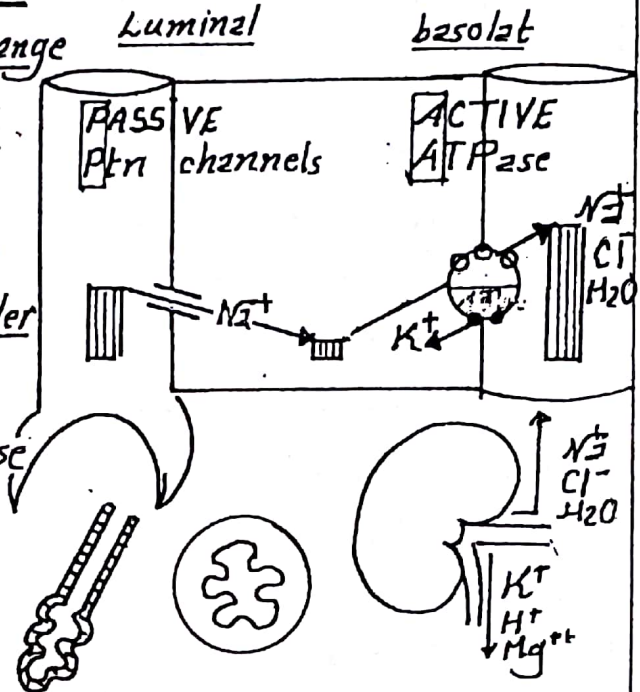
$\text{Na} - \text{K} \text{ ATPase}$

Cl^- & H_2O follow passively

(2) ++ secretion of K^+

[b] I cells : ++ H^+ secretion

[2] On colon, sweat, salivary & gastric glands : ++ Na^+ reabsorp & ++ K^+ secretion



- Control of aldosterone secretion : 4 Aldosterone ++ by:

[1] ++ K^+ plasma level : by 1 mEq

Mechanism ++ conversion of cholesterol to pregnenolone to aldosterone
Depol. of adrenal cell opens Ca^{2+} channels $\rightarrow$ ++ aldosterone release.

[2] Renin - angiotensin system :

Angiotensinogen $\xrightarrow{\text{Renin}}$ Angiotensin I $\xrightarrow{\text{ACE}}$ Angiotensin II.

A II ++ aldosterone by:

Renin secretion is increased by :

Receptors on Z glomerulosa

1

-- ECF volume e.g. hge.

$\rightarrow$ ++ synthesis & secretion

2

Narrowing of renal artery.

early cholesterol to pregnenolone

late corticosterone to aldosterone

3

-- Na^+ -- intake or acute diuresis.

hypertrophy of Z glomerulosa

4

Upright posture for hours.

ANP -- renin & -- AII response

5

++ symp. activity via β receptors.

[3] -- Na^+ plasma level :

by 20 mEq

Initially by macula densa

then by renin angiotensin system (8)

[4] ACTH : not import.

-- ACTH $\rightarrow$ -- Z glomerulosa response to stimuli

Adrenal androgens: DHEA & Androstenedione in tissues → testosterone.

Controlled by ACTH (not gonadotropins).

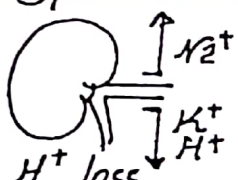
♀ maintain pubic & axillary hair stimulate RBCs production.
♂ effects masked by testicular androgen.

Adrenal estrogens: source Adrenal androgen conversion → estrogen.
source of estrogen in men and postmenopausal women.

Disorders of adrenal cortex

[1] Hypersecretion of mineralocorticoids : 3

(A) Prim. hyperaldosteronism (Conn's syndrome): tumour of Adrenal Cortex

a Hypokalemia 
 Hypokalemic nephropathy polyuria (dilute urine)
 Muscle weakness due to hyperpolarization
 -- Glucose tolerance due to -- insulin secretion
 Metabolic alkalosis → tetany

c Hypernatremia → ++ ECF Hypertension NO EDEMA
 i.e. escape phenomenon due to ++ ANP caused by ++ CVP

(B) Secondary hyperaldosteronism: Ht. failure, liver cirrhosis or nephrosis
 Mech: ++ Renin MARKED EDEMA i.e. no escape phenomenon

(C) Glucocorticoids - remediable (treated) aldosteronism:

Genetic error ++ Z. glomerulosa to ACTH . Ht. Glucocorticoids .

[2] Cushing syndrome

Causes 1 Adrenocortical tumour ACTH independent -- ACTH.

2 Pituitary tumour ACTH dependent ++ ACTH.

3 Treatment with large doses of cortisol.

Features [1] Glucocorticoids effects

(a) Protein catabolism Skin: thin, bruises, hair is thin & poor healing -- immunity



Muscle: Atrophy & weakness.

Bones: Osteoporosis -- formation --> fracture. ++ resorption

(b) FAT : Trunkal obesity : Moon face, buffalo hump.

Purple stria : Stretched vs under skin.

Hyperlipemia & ketosis.

(c) CHO : Hypoglycemia.

Insulin resistant DM.

(d) CNS : Insomnia, euphoria, ++ appetite
++ basic EEG rhythm.



[2] Mineralocorticoids : Hypertension 85% of cases

[3] Androgen excess : Hirsutism Acne

[4] ACTH excess : Pigmentation (ACTH dependent).

[3] Hypersecretion of adrenal androgen (Adrenogenital syndrome)

(A) Intrauterine life : Female pseudohermaphrodite.

Gonads ovaries ♀, Genetic constitution xx ♀ but Genitalia ♂

(B) Prepubertal male : Precocious pseudopuberty no testicular growth.

(C) Adult Female : Female adrenogenital syndrome.

i.e. Masculinization beard, may be baldness, acne and deep voice.

♂ distribution of hair & fat ++ muscle bulk.

Atrophy of uterus & breast & enlarged clitoris and amenorrhoea.

NB In all cases of adrenogenital syndrome : ++ urinary 17 ketosteroids.

Hyposecretion of adrenal cortex (Addison's syndrome).

Causes : autoimmune disease, tuberculosis or cancer.

Effects : [1] -- Glucocorticoids

a Hypoglycemia -- Fasting (--- gluconeogenesis) & -- Post prandial (--- insulin sensitivity)

b Severe muscle weakness, fatigue & loss of weight (--- energy substrate).

c Decreased resistance to stress :

d Pigmentation (gums, p areas & nipple) due to ++ ACTH (--- cortisol).

e ++ eosinophils & lymphocytes and -- neutrophils.

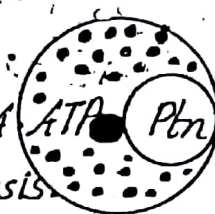
[2] -- Mineralocorticoids :

- a Hyponatremia : Hypotension 100%, Diarrhoea and polyuria .
- b Hyperkalemia : Cardiac arrhythmia & weakness of cardiac contr.
- c H⁺ retention : Mild metabolic acidosis .

[3] -- Adrenal androgen : Anemia & loss of pubic & axillary hair in ♀
NB Addisonian Crisis collapse, shock, hypoglycemia & hyperkalemia.
III IV cortisol, isotonic NaCl infusion. (Emergency) .

Adrenal Medulla Modified sympathetic ganglion.

- Norepinephrine N methyl transferase → Epinephrine 80% .
- Storage Granulated vesicle bound to ATP & chromogranin A .
- Release A potential → ACholine → ++ Ca⁺⁺ Exocytosis .



● Regulation of adrenomedullary secretion :

low in basal level : -- during sleep .

Increased secretion :

1 Emergency situation :

2 Stressful stimuli :

a Hypo thermia & cold .

b Hypo glycemia .

c Hypo tension & hge .



Leading to

++ MR .

++ Bl. glucose .

VC (in presence of control) .

● Adreno. medullary tumour (Pheochromocytomas) .

- Most types : secrete norepinephrine .

→ episodic or sustained Hypertension

- Some types : secrete epinephrine .

→ Hyperglycemia, glycosuria & elevated MR . End

● Actions of epinephrine and norepinephrine : 3

- [1] CVS [a] Heart Both hormones via β_1 ++ rate, force & excitability,
 [b] Bl vs Norepinephrine α_1 $\rightarrow$ ++ TPR.
Epinephrine VD β_2 $\rightarrow$ -- TPR.
 VC others.

[c] <u>Effect on</u>	<u>Systolic P</u>	<u>Diastolic P</u>	<u>ABP</u>	<u>HR</u>	<u>COP</u>
<u>Norepinephrine</u>	++	++	++	--	--
<u>Epinephrine</u>	++	---	--	++	++

- [2] CNS [a] Both alertness due to activation of RF.
 [b] Epinephrine anxiety and fear.

[3] Metabolism :

- [a] Blood glucose Increased.
 1 Activate hepatic phosphorolase via β & $\alpha \rightarrow$ glycogenolysis $\rightarrow$ ++ bl glucose
 2 " muscle " via β & α $G6P \rightarrow$ pyruvate $\rightarrow$ lactate
 lactate diffuses in blood to liver & converted to glycogen.
 3 Catecholamines via β receptors ++ insulin & glucagon secretion
 α " -- " " "

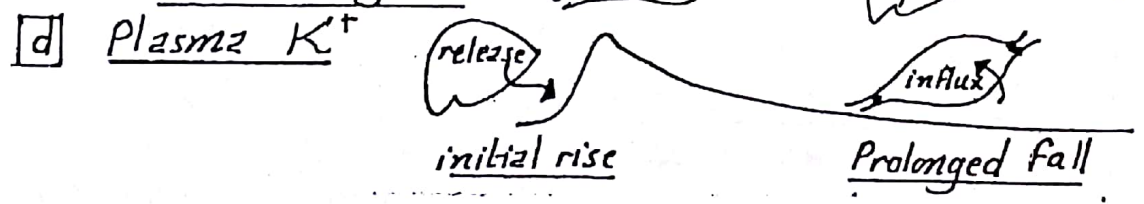
Net effect -- insulin & ++ glucagon $\rightarrow$ ++ bl glucose

4 Epinephrine -- peripheral utilization of glucose.

[b] Adipose tissue Lipolysis epinephrine via lipase.

[c] Metabolic rate ++ MR via :

- 1 -- Heat loss Cutaneous VC. $\odot$
 2 ++ Heat gain ++ muscle tone & ++ hepatic oxid. of lactate.

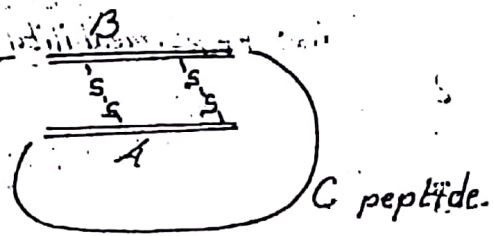


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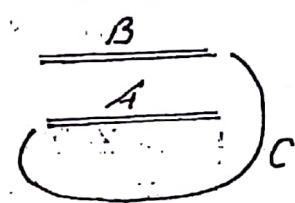
Insulin

- Structure: Polypeptide A & B chains linked by disulfide bridges.
- Synthesis: signal

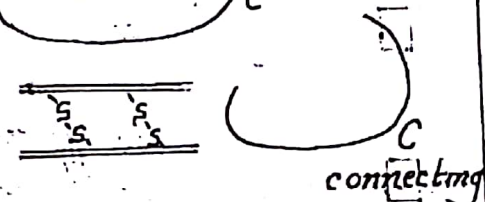
• In ribosomes
prepro insulin
4 peptides



• In endoplasmic reticulum
pro insulin
3 peptides



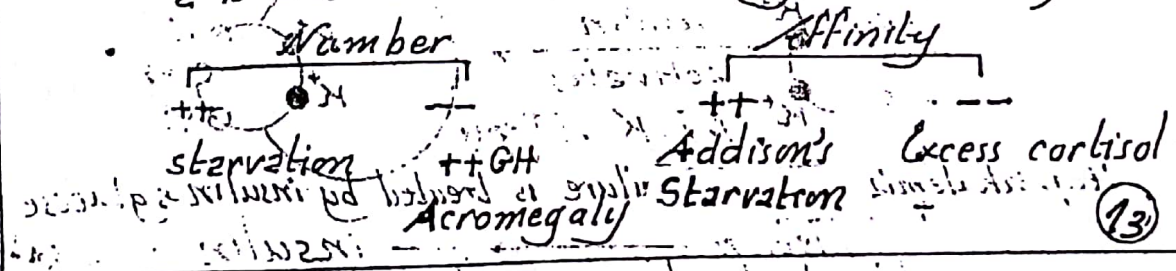
• In Golgi complex
insulin
+ C peptide



- Secretion:
 - Moved through microtubules to cell membrane.
 - Released by exocytosis which needs Ca^{++} .
 - 90-97% as insulin + equimolar amount of C peptide.
 - rest - mostly proinsulin - little biological activity.

- Transport & inactivation:
 - Insulin circulates free in plasma ($\frac{1}{2}$ life 5 mins).
 - Inactivated by insulinase (does not pass in urine).
- Insulin like substances in blood: weaker than insulin.
 - IGF I: Small amount Free (low MW fraction).
 - IGF II: Large amount bound to pln. (High MW fraction)

- Insulin receptors: 4 subunits held by disulfide link.
 - 2 α subunits outside bind to insulin.
 - 2 β subunits inside (tyrosine kinase).

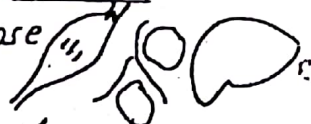


- Cellular effects mem, cytoplasm or nucleus

Rapid

++ membrane permeability to glucose
Also ++ permeability to aa, K^+ & PO_4

Seconds



Intermediate

Phosphorylation & dephosphorylation of enzymes

Minutes

Delayed

++ or -- DNA & mRNA to form new proteins

Hours

- Glucose transporters

1 Secondary active transport

Na^+ -glucose cotransport

i.e. SGLT₁

&

SGLT₂

in intestine & renal tubules

2 Facilitated diffusion

i.e. Seven plz transporters GLUT₁ - GLUT₇

GLUT₄ in cytoplasm of muscles and adipose tissue

Insulin moves it to cell mem. by exocytosis

Other glucose transporters are not sensitive to insulin

Exercise moves GLUT₄ vesicles to cell mem. → -- bl. sugar

- Insulin stimulated glucose uptake

1 In muscles & adipose tissues

++

GLUT₄

2



++ glucokinase

→

++

G₁-G₂ for free glucose

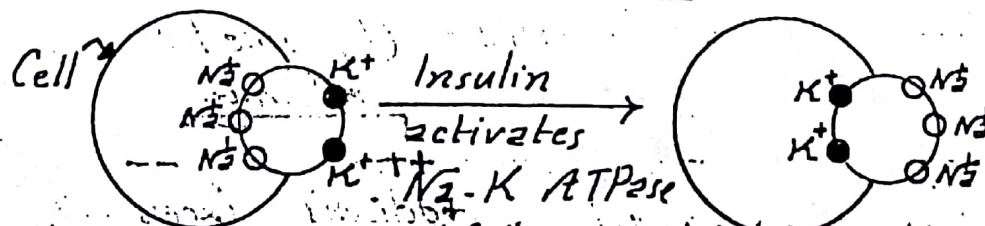
3

In brain & BBB - RBCs - Intestine and kidney

Insulin DOES NOT stimulate glucose entry

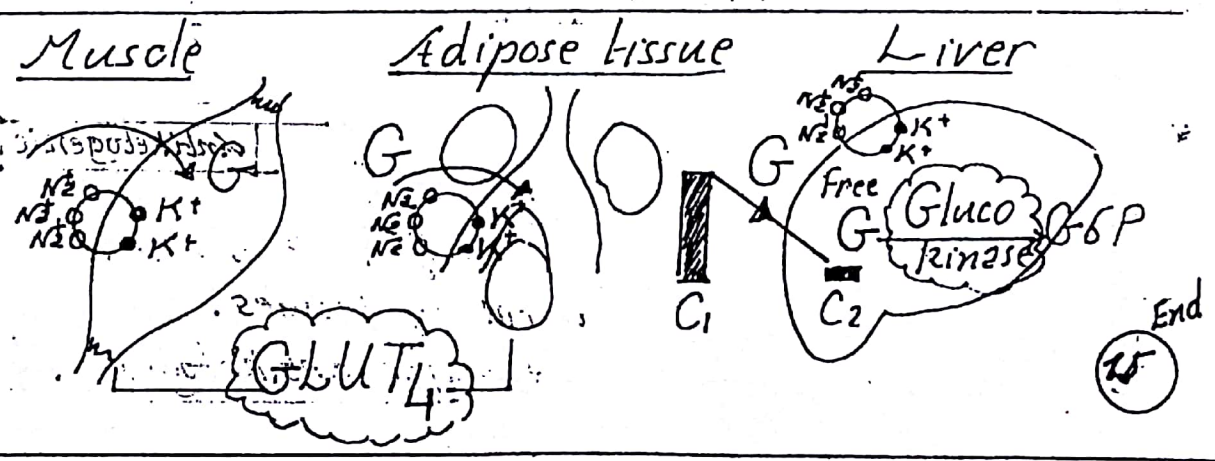
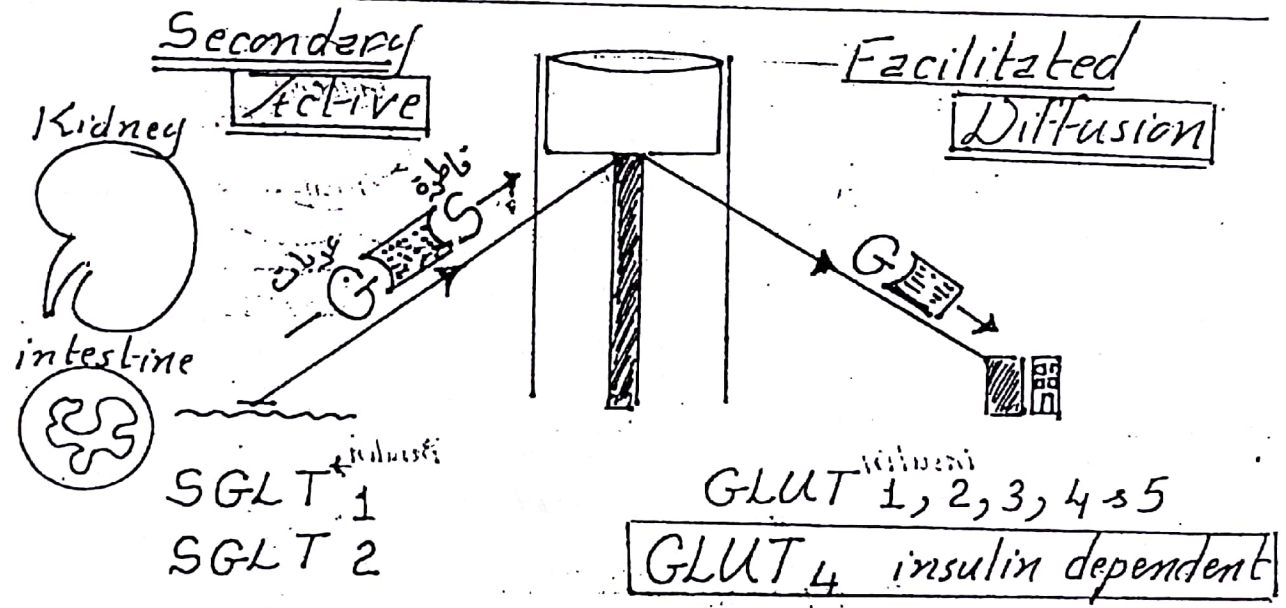
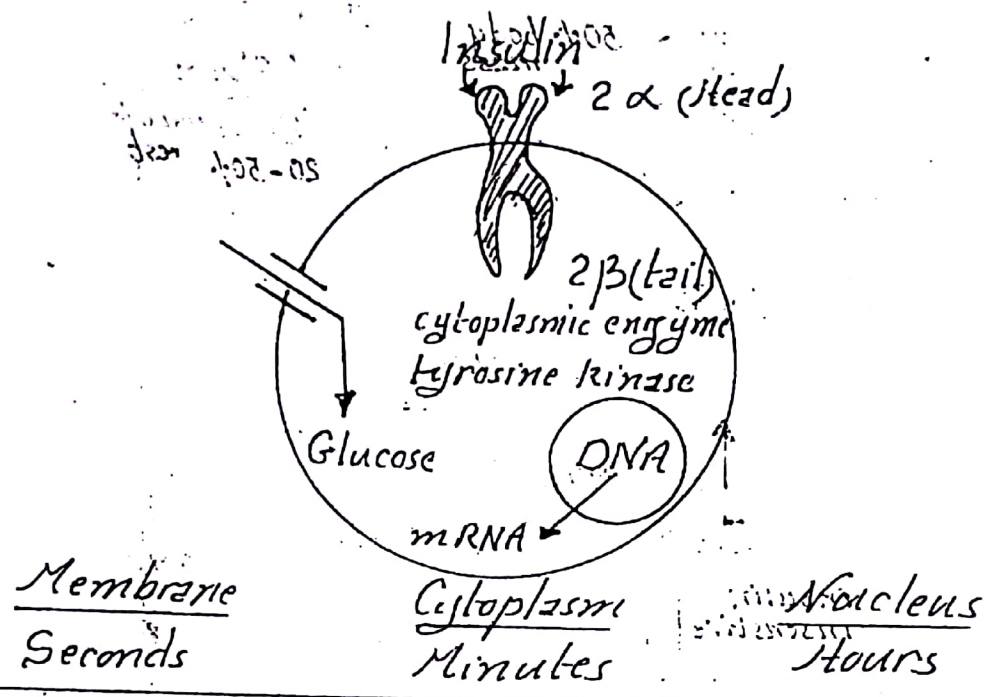
It occurs by FD GLUT₁, 2, 3, 5 or SGLT₁ & SGLT₂

- Relation of insulin to potassium:



Hyperkalemia & renal failure is treated by insulin & glucose
Also, K^+ depletion → -- insulin (24) End
e.g. thiazide diuretic

Mechanism of action Cellular effect

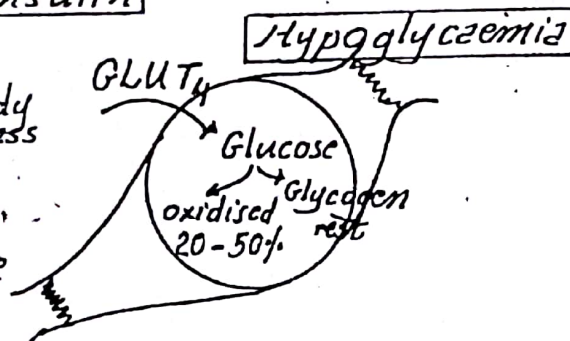


End
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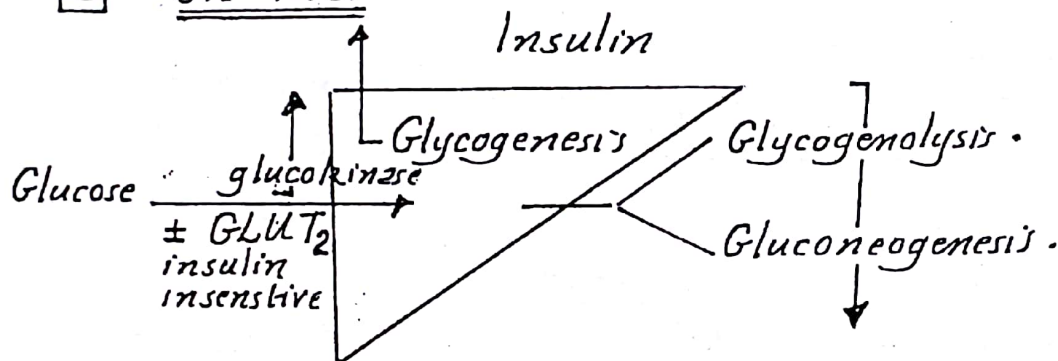
• Metabolic actions of insulin

① On CHO

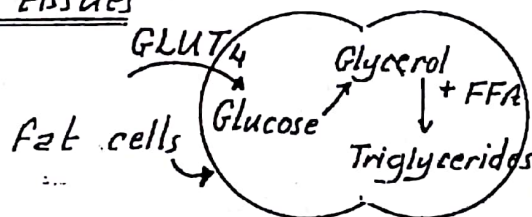
- A On muscle 50% body mass
- Insulin
- ++ GLUT₄
 - -- FFA uptake



B On liver

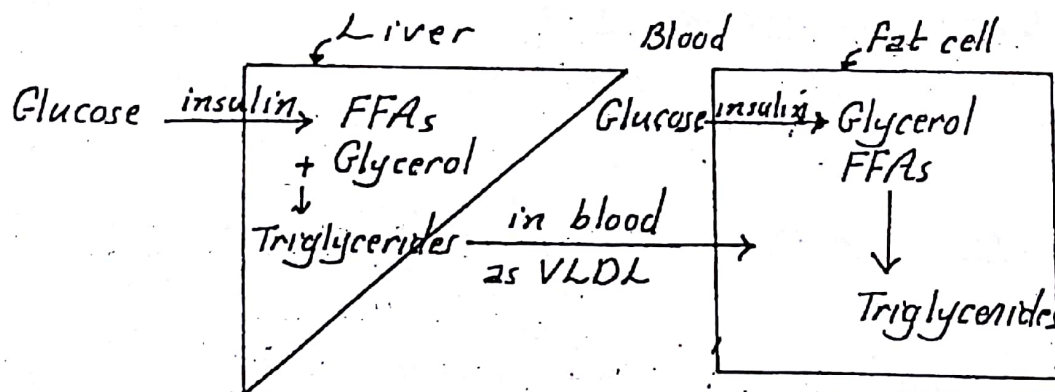


C On adipose tissues



② On Fat

Lipogenesis



Antiketogenic

Insulin inhibits Lipolysis

-- Lipase --> -- Ketoacids.

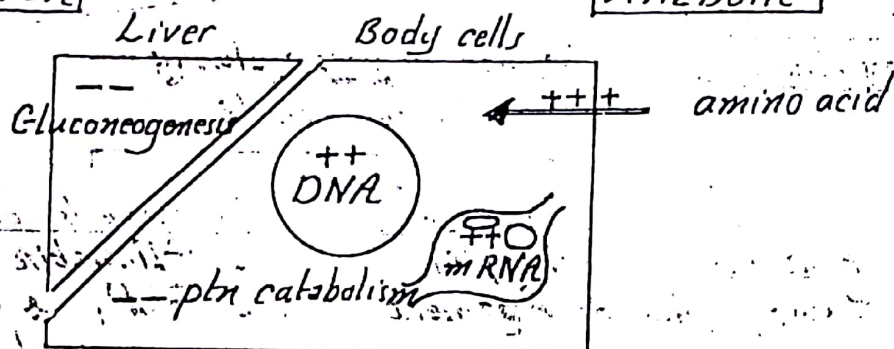
++ use of ketoacids by tissues.

i.e insulin is the major antiketogenic.

⑩

③ On Ptn

Anabolic

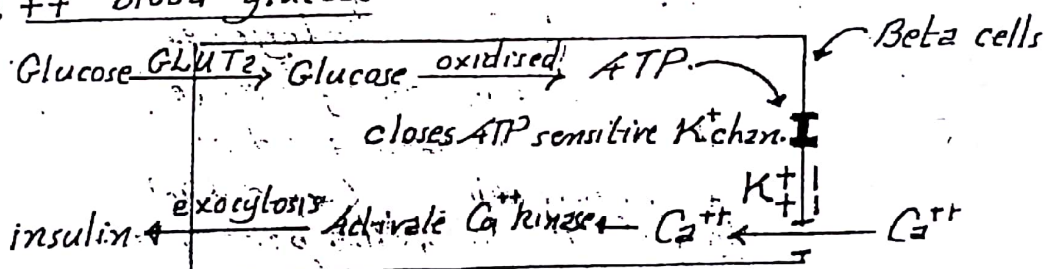


④ On Growth

- a Direct effect: synthesis of macromolecules as GH.
 b Indirect effect: stimulates transcription of related gene of IGF₁.

Control of insulin secretion

1 ++ blood glucose



2 ++ Amino acids e.g. arginine ++ glucose stim.

3 Gastro intestinal hormones e.g. GIP ++ glucose stim.

4 Islet hormones — Glucagon ++
Somatostatin --

5 Other hormones e.g. Cortisol, GH ... etc ++ insulin secretion

Insulin -ve → -- insulin "

leptin -- insulin "

6 cAMP : ++ intracell Ca²⁺ ++ insulin "

7 Catecholamines: α -- β ++ insulin "

8 Autonomic nerves — vagus (M₄) ++ insulin "symp. α₂recep -- insulin "

Glucagon

Hyperglycaemic hormone.

• Synthesis

Human preproglucagon
processed to

- In α cell of pancreas
- Glucagon Polypeptide
 - Major proglucagon fragment

- In L cells of GIT
- Glicentin
 - GLP₁ & GLP₂
↳ stimulator of insulin

• Actions

1 On CHO

- Liver glycogenolysis

1 μ g/kg glucagon
→ ++ bl. glucose
20 mg/l in 20 min

Hyperglycaemia

2 types of receptors

++ cAMP activate phospholipase C
ptn kinase A ++ cytoplasmic Ca^{++}

- gluconeogenesis

2 On Fat

Lipolysis & ketogenesis

3 On Ptn

++ aa uptake by liver cells

4 Calorigenic

due to hyperglycaemia & deamination of aa

5 Heart

++ inotropic (++ cAMP)

6 Stimulates secretion of insulin, Gl & panc. somatostatin

• Regulation

Secretion is increased by: 6 Secretion is decreased by: 6

1 -- blood glucose

① ++ blood glucose & FFA & ketones

2 ++ blood amino acid

② Insulin

3 GIH i.e. CCK & gastrin

③ GABA

i.e. ptx meal

4 Sympathetic stimulation
via β receptors i.e. cAMP

④ Sympathetic stim.
via α adrenergic recep

5 Heavy exercise

⑤ Somatostatin

via symp & -- bl. glucose

⑥ Secretin

6 Stress & infection

via symp.

End

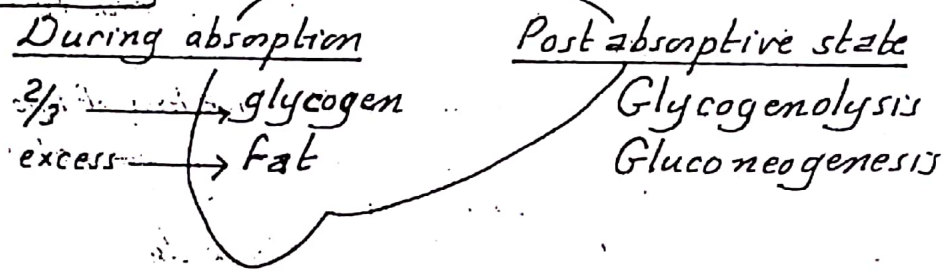
(18)

Somatostatin

- Actions: prevents rapid exhaustion of food.
 - 1 $\rightarrow$ insulin, glucagon & panc polypeptide secr.
 - 2 $\rightarrow$ motility of stomach, intestine & gall bladder.
 - 3 $\rightarrow$ secretion and absorption from the GIT.
- Regulation: ingestion of food $++$ somatostatin i.e.
 - 1 $++$ blood glucose, amino acids & fatty acids.
 - 2 $++$ gastro intestinal hormones e.g CCK.

Glucose Homeostasis i.e regulation of blood glucose.
Glucostatic mechanisms: Liver and hormones.

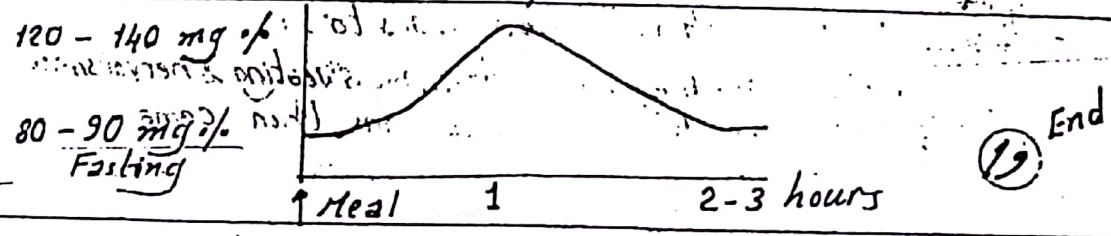
1 Liver



2 Hormones

- (a) Insulin & glucagon Feed back.
 - Hypoglycaemia $\rightarrow ++$ insulin $\rightarrow --$ bl. glucose
 - Hypoglycaemia $\rightarrow ++$ glucagon $\rightarrow ++$ bl. glucose
- (b) Severe hypoglycaemia Epinephrine.
 - $\rightarrow$ viz hypoth $\rightarrow ++$ epinephrine $\rightarrow$ glycogenolysis
- (c) Prolonged hypoglycaemia (hours to days)

<u>GH</u>	<u>Cortisol</u>
- Glycogenolysis.	- Gluconeogenesis.
- Lipolysis.	- Lipolysis.
- -- number of insulin receptors.	- -- affinity of insulin to its receptors.



Diabetes Mellitus DM

- Cause : Relative or absolute insulin deficiency.
- Predisposing factors : Hereditary Obesity -- number of insulin R.
- In animals : DM is caused by Alloxan, Antiinsulin Ab & pancreatectomy
- Types : Type I IDDM .. Autoimmune Ab destroy β cells before 40y.
Type II NIDDM Insulin resistance After 40y most common.
Causes 1 insulin resistance $\rightarrow$ ++ insulin $\rightarrow$ β cells exhaustion
 2 Genetic defect IRS 1/5', GLUT₄, Glucokinase, Insulin R.

● Manifestations :

- 1 CHO Hypoglycemia leads to ++ OP $\rightarrow$ cellular dehydration.
 Glycosuria $\rightarrow$ Polyuria $\rightarrow$ Polydipsia $\rightarrow$ ++ urinary K^+ & Na^+ loss.
 Polyphagia Satiety centre fails to use glucose (no insulin).
 - 2 FAT Excessive utilization of fat results in :
 Lipolysis $\rightarrow$ ++ plasma FFAs (double) $\rightarrow$ Ketosis.
 ++ triglycerides ++ cholesterol, ++ VLDL & ++ LDL.
 - 3 Ptn Excessive catabolism and -- Synthesis.
 loss of weight Aschemia ++ Gluconeogenesis.
- N.B Careful control of DM by insulin is based on measuring of HbA_{1c}

Hypoglycemia

- Causes Overdose of insulin, Insulinoma, tumour secreting excess IGF_{II}.
 - Manifestations 1 Autonomic changes: palpitation, sweating & nervousness.
 2 At lower glucose level: Hunger, confusion & cognitive abnormalities.
 3 At even lower glucose level: lethargy, coma, convulsions & death.
- N.B Hypoglycemia is dangerous; Glucose is the only fuel used by brain & retina.
Hypoglycemia is harmful $\rightarrow$ infection.

Good Luck

End
(20)